Diet, lifestyle factors, metabolic health and risk of Parkinson's disease – A prospective cohort study

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ACADEMIC DISSERTATION

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Abstract

Parkinson's disease (PD) is a movement disorder with progressive neurodegeneration. As populations continue to age, the burden of this disease will increase. Although both environmental and genetic factors seem to play a major role in the etiology of PD, the causes of the neuronal death underlying the disease remains largely unknown. As curative treatment for PD remains a challenge, knowledge to aid in the development of prevention tools is crucial. Thus, identifying risk factors, especially modifiable ones, is essential.

The aim of the present study was to examine the prediction of dietary, lifestyle and metabolic factors on PD risk in a cohort study design.

This study included men and women free from PD at baseline of the Finnish Mobile Clinic Health Examination Survey (FMC, 1966–1972, n=4,524), the Follow-up study of the FMC (FMCF, 1973–1975, n=6,715), and the Mini-Finland Health Survey (1978–1980, n=4,828). Over a follow-up of 22–41 years, the PD cases (International Classification of Diseases 10, code G20, from the World Health Organization) in the FMC (n=85), the FMCF (n=101), and the Mini-Finland Health Survey (n=89) were identified through linkage with the nationwide Drug Reimbursement Register of Social Insurance Institution.

Information on lifestyle factors, socioeconomic background, and physiological and biochemical determinants were collected by questionnaires, interview, and health examinations at the baselines of these three surveys. Dietary intake was assessed with a 1-year dietary history interview in the FMC.

The exposure factors studied here were diet (individual food groups and items, as well as a diet quality index), leisure-time physical activity, smoking, alcohol consumption, coffee consumption, body mass index, blood pressure, as well as concentration of serum HDL cholesterol, serum triglyceride, fasting plasma glucose, and serum total cholesterol.

Cox's proportional hazards model was used to estimate the strength of association between the exposure factors and PD risk. Potential confounding factors were adjusted by inclusion in multivariate models.

Most of the individual food groups and items, as well as the diet quality, did not predict the risk of PD. There were few exceptions however, e.g. high consumption of milk was associated with increased PD risk in women. Smoking, heavy consumption of coffee, as well as heavy leisure-time physical activities were associated with decreased PD risk. Alcohol consumption had no clear association with PD risk. Those who had metabolic syndrome had a reduced risk of PD, mainly due to high serum triglyceride and fasting plasma glucose concentration. Serum HDL cholesterol, serum total cholesterol concentration, and blood pressure, however, had no association with PD risk. After taking into account the potential preclinical disease phase, we observed that obesity might increase the risk of PD.

In conclusion, diet and other lifestyle factors, as well as metabolic health, may predict the risk of PD. The prospective design of this study is a strength when providing etiologic clues for unraveling the mystery of PD. The overall evidence from the literature is, however, currently too sparse for making recommendations for public health purposes to prevent PD. In the future, perhaps, the results of the present study, as well as previous studies, may be used in clinical practice when planning tools for the early identification of PD patients.

Keywords: Parkinson's disease, cohort study, diet, lifestyle factors, metabolic health

Tiivistelmä

Parkinsonin tauti on hermosolujen etenevästä tuhoutumisesta johtuva liikehäiriösairaus. Väestön ikääntyessä taudin ennustetaan kuormittavan yhä useampia. Parkinsonin taudin syntyyn vaikuttavat sekä geneettiset että ympäristötekijät, mutta varsinaista syytä taudin aiheuttavalle hermosolujen tuhoutumiselle ei vielä tunneta. Toistaiseksi Parkinsonin tautia ei pystytä parantamaan, joten tietoa Parkinsonin taudin ehkäisemiskeinojen löytämiseksi tarvitaan. Siksi on oleellista tunnistaa etenkin sellaiset taudin riskitekijät, joihin on mahdollista vaikuttaa.

Tämän tutkimuksen tavoitteena oli selvittää kohorttiasetelmassa, ennustavatko ravitsemus-, elintapa- tai metaboliset tekijät Parkinsonin taudin riskiä.

Tutkimusaineisto koostui Autoklinikka-tutkimuksiin osallistuneista miehistä ja naisista, jotka eivät tutkimuksen alkutilanteessa sairastaneet Parkinsonin tautia (Autoklinikan moniseulontatutkimus, AK, vuosina 1966–1972, n=4 524; Autoklinikan uusintatutkimus, AU, 1973–1975, n=6 715; sekä Mini-Suomi -tutkimus, MS, 1978–1980, n=4 828). Parkinsonin tautiin sairastuneet henkilöt (Maailman terveysjärjestön ICD-10 -tautiluokitus, koodi G20) tunnistettiin 22–41 vuoden seurannassa Kansaneläkelaitoksen ylläpitämästä, lääkkeiden erityiskorvausoikeuden saaneita koskevasta rekisteristä (AK, n=85; AU, n=101; ja MS, n=89). Tutkimuksessa kerättiin kyselylomakkeiden, haastatteluiden ja terveystarkastusten avulla tietoa elintapatekijöistä, sosioekonomisesta taustasta, sekä fysiologisista ja biokemiallisista tekijöistä kaikkien kolmen tutkimuksen alkutilanteessa. Autoklinikan moniseulontatutkimuksessa tutkittavien edeltäneen vuoden ruoankäyttöä selvitettiin ruokavaliohaastattelulla.

Tämä tutkimus tarkasteli seuraavien tekijöiden yhteyttä riskiin sairastua Parkinsonin tautiin: ruokavalio (yksittäiset ruoka-aineryhmät ja ruoka-aineet, sekä ruokavalion laatua kuvaava indeksi), vapaa-ajan liikunta, tupakointi, alkoholin ja kahvin kulutus, painoindeksi, verenpaine, sekä seerumin HDL-kolesterolin, seerumin triglyseridien, plasman paastoglukoosin ja seerumin kokonaiskolesterolin konsentraatio.

Altistemuuttujien ja Parkinsonin taudin välisen yhteyden voimakkuutta arvioitiin Coxin mallin avulla. Mahdolliset sekoittavat tekijät vakioitiin sisällyttämällä ne monimuuttujamalleihin.

Suurin osa yksittäisistä ruoka-aineryhmistä tai ruoka-aineista, samoin kuin ruokavalion laatu, eivät olleet yhteydessä Parkinsonin taudin riskiin. Tästä havaittiin kuitenkin muutamia poikkeuksia, esimerkiksi naisilla suurempi maidon kulutus oli yhteydessä kohonneeseen riskiin sairastua Parkinsonin tautiin. Runsas vapaa-ajan liikunta ja kahvin juonti sekä tupakointi puolestaan pienensivät riskiä sairastua Parkinsonin tautiin. Alkoholin kulutus ei ollut selkeästi yhteydessä Parkinsonin tautiin. Henkilöillä, joilla oli metabolinen syndrooma, oli pienentynyt riski sairastua Parkinsonin tautiin, mikä johtui pääasiassa kohonneista seerumin triglyseridiarvoista ja plasman paastoglukoosiarvoista. Seerumin HDL-kolesteroli tai kokonaiskolesteroli eivät olleet yhteydessä Parkinsonin tautiin, kuten ei ollut myöskään verenpaine. Kun analyyseissä huomioitiin mahdollinen prekliinisen taudin vaikutus, havaittiin että lihavuus saattaa lisätä riskiä sairastua Parkinsonin tautiin.

Yhteenvetona voidaan todeta, että ruokavaliolla tai muilla elintapatekijöillä saattaa olla yhteyttä riskiin sairastua Parkinsonin tautiin. Tämän tutkimuksen prospektiivinen asetelma on vahvuus etsittäessä etiologisia vihjeitä Parkinsonin taudin arvoituksen ratkaisemiseksi. Tällä hetkellä tutkimusnäyttö on vielä riittämätöntä, jotta voitaisiin laatia suosituksia toimista Parkinsonin taudin ehkäisemiseksi. Tämän tutkimuksen sekä aikaisempien tutkimusten tuloksia voidaan hyödyntää kliinisessä potilastyössä, kun suunnitellaan menetelmiä Parkinson taudin varhaiseksi tunnistamiseksi.

Avainsanat: Parkinsonin tauti, kohorttitutkimus, ruokavalio, elintapatekijät, metabolinen terveys

Contents

List of original publications

This dissertation is based on the following original publications referred to in the text by their Roman numerals:

I Sääksjärvi K, Knekt P, Lundqvist A, Männistö S, Heliövaara M, Rissanen H, Järvinen R. A cohort study on diet and the risk of Parkinson's disease: the role of food groups and diet quality. Br J Nutr. 2013;109(2):329-37.

II Sääksjärvi K, Knekt P, Männistö S, Lyytinen J, Jääskeläinen T, Kanerva N, Heliövaara M. Reduced risk of Parkinson's disease associated with lower body mass index and heavy leisure-time physical activity. Eur J Epidemiol. 2014;29(4):285-92.

III Sääksjärvi K, Knekt P, Rissanen H, Laaksonen MA, Reunanen A, Männistö S. Prospective study of coffee consumption and risk of Parkinson's disease. Eur J Clin Nutr. 2008;62(7):908-15.

IV Sääksjärvi K, Knekt P, Männistö S, Lyytinen J, Heliövaara M. Prospective study on the components of metabolic syndrome and incidence of Parkinson’s disease. Parkinsonism Relat Disord. 2015 Oct;21(10):1148-55.

Abbreviations

AHEI	Alternate Healthy Eating Index
aMED	alternate Mediterranean Diet Score
BMI	body mass index
CI	confidence interval
CV	coefficient of variation
CVD	cardiovascular disease
d	day
DBP	diastolic blood pressure
EPIC	European Prospective Investigation into Cancer and Nutrition
FMC	Finnish Mobile Clinic Health Examination Survey
FMCF	Finnish Mobile Clinic Follow-up Survey
g	gram
h	hour
HDL	high-density lipoprotein
ICC	Intraclass correlation coefficient
ICD	International Classification of Diseases (from the World Health Organization)
kg	kilogram
LDL	low density lipoprotein
m	meter
mAHEI	modified Alternate Healthy Eating Index
mmHg	millimeter of mercury
mmol/L	millimole per liter
PD	Parkinson's disease
RR	relative risk
SBP	systolic blood pressure
SD	standard deviation
SII	Social Insurance Institution
VLDL	very-low-density lipoprotein

1 Introduction

Parkinson's disease (PD) is a complex neurodegenerative disease wherein progressive death of dopaminergic neurons leads to a movement disorder with numerous non-motor symptoms (see Kalia and Lang 2015a). Although PD was first described almost two centuries ago, the conceptualization of the disease continues to evolve. The understanding of pathogenesis of the disease is expanding, but there is no treatment that could prevent or delay the progression of the disease.

Non-motor symptoms often manifest in early PD before the motor symptoms, and are present during the entire disease course. They include olfactory dysfunction, cognitive impairment, psychiatric symptoms, sleep disorders, autonomic dysfunction, pain, and fatigue (see Kalia and Lang 2015a). There are estimates that motor symptoms first appear when about 30% of substantia nigra dopamine neurons are lost (see Cheng et al. 2010). The principal motor symptoms include bradykinesia, muscular rigidity, rest tremor, and postural and gait impairment (see Jankovic 2008).

The motor symptoms related to dopamine deficiency in PD can be relieved with several drugs, of which the oral replacement of dopamine by its precursor levodopa is the most effective. Other dopaminergic drugs include direct-acting dopamine agonists and agents, such as monoamine oxidase B and catechol-O-methyltransferase inhibitors, that enhance dopamine's effect through the inhibition of distinct metabolic pathways. However, the broad range of symptoms and treatment-related complications, especially in late-stage PD, contribute to substantial disability (see Kalia and Lang 2015a). Both the motor and non-motor symptoms vary between PD patients, and different subtypes of PD have been suggested (see Kalia and Lang 2015a). Altogether, due to the progressive nature of the disease, PD is characterized by a worsening of the symptoms, eventually leading to a reduced quality of life, increased need for institutional care, and increased mortality (see Kalia and Lang 2015a).

Neurodegenerative diseases are the seventh leading cause of death and a major cause of disability in high-income-countries (see Lopez et al. 2006). There are estimates that in 2005 the number of individuals (aged 50 and above) with PD was between 4.1 and 4.6 million in 15 countries around the world (Western Europe's 5 most and the world's 10 most populous nations), and will grow to between 8.7 and 9.3 million by 2030 (see Dorsey et al. 2007). In Finland, the estimated number of PD patients is currently about 17,000, based on the number of individuals receiving the Social Insurance Institution's reimbursement right code 110 for PD ("Tilastotietokanta Kelasto", Kansaneläkelaitos. <http://www.kela.fi/kelasto>. January 21st 2016). With the world's populations aging, the importance of PD as a public health issue is expected to increase.

Both the human and economic burden of PD are substantial. Despite the several causative monogenetic mutations that have recently been discovered, the etiology of PD is multifactorial in about 90% of cases, with both non-genetic (environmental) and genetic factors seeming to play a major role (see de Lau and Breteler 2006a). Thus, it is essential to identify modifiable risk factors and to clarify under what circumstances changes in them would optimally reduce the risk of PD. Epidemiological studies on PD could help in identifying targets for research into the etiology of PD, and in developing prevention strategies. Furthermore, epidemiological studies may help in developing tools for early detection of the disease. The premotor phase of the disease provides a potential window of opportunity, during which a disease-modifying therapy – if available – could be administered (see Siderowf and Lang 2012).

Several hypotheses have been presented suggesting that dietary, lifestyle, and biological factors may provide protection against PD (see Wirdefeldt et al. 2011; see de Lau and Breteler 2006a). The overall

epidemiological evidence, however, is still scarce. Large prospective cohort studies with proper exposure assessments and PD ascertainment are needed. The three cohorts used in this study, the Finnish Mobile Clinic Health Examination Survey, the Finnish Mobile Clinic Follow-up Survey, and the Mini-Finland Health Survey, were well-suited for this purpose due to their long follow-up periods and relatively large sample sizes. Therefore, the aim of this study was to predict the risk of PD by dietary, lifestyle, and metabolic factors in a prospective cohort study design. Regarding diet, the aim was to assess the diet as a whole. Thus, this study included dietary assessments at both the summary level (utilizing a diet quality index) as well as at the level of individual food groups and items (components of the index). Furthermore, lifestyle factors selected for this study included leisure-time physical activity, smoking, alcohol consumption, and coffee consumption. Metabolic health was approached by examining both obesity as well as metabolic syndrome and its components.

2 Review of the literature

2.1 Parkinson's disease

Parkinson's disease (PD), originally described by James Parkinson in 1817, is the most common neurodegenerative disease after Alzheimer's disease (see Dorsey et al. 2007). PD is characterized by the progressive death of selected but heterogeneous populations of neurons, including the dopaminergic neurons of the pars compacta of the substantia nigra, leading to a loss of dopamine in the striatum which accounts for most of the classic clinical motor features of PD (see Lang and Lozano 1998).

It appears that multiple different pathogenic pathways and mechanisms can ultimately lead to PD, and both genetic and environmental factors are believed to play a central role (Bronstein et al. 2009). The exact pathogenic mechanisms underlying the neurodegeneration remain largely unknown, but some of the pathways that have been implicated so far include mitochondrial dysfunction, oxidative stress, kinase pathways, calcium dysregulation, inflammation, protein handling, and prion-like processes (see Schapira et al. 2014).

2.1.1 Prevalence and incidence

PD is an age-related disease, being rare before the age of 50. The prevalence increases with age, with up to 4% in the highest age groups (80-90 year olds) (see de Lau and Breteler 2006a). The literature, however, presents varying prevalence and incidence rates for PD, partly due to geographical and demographic factors. In addition, methodological differences produce varying rates, for example, utilizing varying diagnostic criteria or case-finding strategies (registry diagnosis vs. door-to-door survey) (see Wirdefeldt et al. 2011). A review based on 12 US and European studies estimated that the prevalence of PD among people 65 years or older was 950 per 100,000 (see Hirtz et al. 2007). The median incidence rate based on 8 studies in developed countries was 14 per 100,000 person-years for all age groups, and 160 per 100,000 person-years when restricted to individuals aged 65 years and above (see Hirtz et al. 2007). Due to the increased global life expectancy, the burden of the disease has grown and will likely continue to do so (see Dorsey et al. 2007).

2.1.2 Diagnosis of PD

The diagnosis of PD is based on clinical criteria, with rest tremor, bradykinesia, rigidity, and postural instability generally considered to be the cardinal signs (see Jankovic 2008). Furthermore, other clinical features, including secondary motor symptoms and non-motor symptoms, may cause severe disability in patients with advanced disease. The Hoehn and Yahr scale, or the Unified Parkinson's Disease Rating scale, are commonly used to provide assessment of disease progression, disability, and impairment (see Jankovic 2008).

The established diagnostic criteria have been developed by the UK Parkinson's Disease Society Brain Bank (Table 1) and the National Institute of Neurological Disorders and Stroke (see Gelb et al. 1999). However, the clinical diagnosis of PD can be challenging, and requires expertise in differentiating it from related disorders. Currently, imaging techniques can aid in this task, but a reliable diagnostic test for PD remains to be found. While potential neuroimaging and pathological markers are being explored and tested, it may be that some combination of imaging, and biochemical and genetic biomarkers are required (see Kalia and Lang 2015a).

Table 1. UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria. Adapted from following reviews: Kalia and Lang 2015a; Jankovic 2008; and Gelb et al. 1999.

Step 1: Diagnosis of parkinsonian syndrome
Bradykinesia (i.e., slowness of initiation of voluntary movement with progressive reduction in speed and amplitude of repetitive actions), plus one or more of the following features:
• Muscular rigidity
• 4–6 Hz rest tremor
• Postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction
Step 2: Exclusion criteria for Parkinson's disease
At least one of the following features suggests an alternate diagnosis:
• 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
• 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine exposure
• Negative response to large doses of levodopa (if malabsorption excluded)
• More than one affected relative*
• Sustained remission
• Strictly unilateral features after 3 years
• Early severe autonomic involvement
• Early severe dementia with disturbances of memory, language, and praxis
• Oculogyric crises
• Supranuclear gaze palsy
• Babinski sign
• Cerebellar signs
• Presence of a cerebral tumour or communicating hydrocephalus on CT scan or MRI
Step 3: Supportive prospective positive criteria for Parkinson's disease
At least three of the following features:
• Unilateral onset
• Rest tremor present
• Progressive disorder
• Persistent asymmetry affecting the side of 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

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging.
*This criterion is generally no longer applied.

Typically, however, as a gold standard, post-mortem confirmation is required for a definite diagnosis of PD. Thus, clinical criteria can lead to a diagnosis of probable PD at best. The pathological features of PD include loss of dopaminergic neurons within the substantia nigra pars compacta and the presence of the Lewy pathology, an intracellular aggregation of abnormally folded α-synuclein proteins (see Kalia and Lang 2015a).

In epidemiological studies, the diagnosis of PD is generally based on clinical criteria. A diagnosis of probable PD was confirmed in 83% of patients when re-evaluated according to strict clinical diagnostic criteria (the UK Parkinson's Disease Society Brain Bank criteria) (Schrag et al. 2002). Another study suggested that the accuracy of the established clinical criteria was up to 90%, when confirmed with neuropathological examination (see Hughes et al. 2001).

The slow progression of PD creates further challenges to epidemiologic investigation. The exact time of onset of the pathophysiologic process of PD in any individual cannot be determined. The mean age of symptom onset was from 60 to 65 years in eight individual studies and over 65 years in a review of five studies (see Twelves et al. 2003). There are suggestions that the non-motor symptoms in PD could begin,

in many instances, decades before the onset of motor symptoms (see Gaig and Tolosa 2009). The early premotor symptoms, such as olfactory deficit, constipation, sleep disorders, depression, and anxiety (see Siderowf and Lang 2012), are likely to influence individual's behavior. Thus, the possibility that underlying preclinical PD may alter or mask the associations observed in epidemiological studies should be acknowledged.

2.2 Epidemiological studies on the risk of PD

2.2.1 An overview of PD epidemiology

There are few reviews providing an insight into the broad spectrum of research on the epidemiology of PD (see Wirdefeldt et al. 2011; see de Lau and Breteler 2006a). Several risk and protective factors for PD have been proposed on the basis of presumed pathogenic mechanisms of the disease (Figure 1). The dietary, lifestyle, and metabolic factors will be reviewed in more detail in following chapters; other factors are briefly mentioned below.

Despite the large number of studies examining PD and occupational exposures, causal relationships have not been established (see Wirdefeldt et al. 2011). The factors grouped under 'pre-existing medical conditions', for example metabolic factors and dementia, are interesting as some of them could also be interpreted as early manifestations of PD. Ultimately, the epidemiologic evidence for most of the proposed risk or protective factors is inconclusive.

A large number of genetic association studies of PD have been published. The known PD genes, however, are estimated to account for only a small proportion of the PD cases occurring at the population level (see Wirdefeldt et al. 2011). Furthermore, genetic heterogeneity complicates the research on new PD genes and loci. In addition, there is little information on gene-environment interactions in PD (see Wirdefeldt et al. 2011).

The majority of studies regarding PD epidemiology have been case-control studies. The meta-analysis by Hernan et al. (2002) included 44 case-control and four cohort studies on smoking and PD. The systematic review by Ishihara and Brayne (2005) included 33 case-control studies and seven cohort studies, with each study only looking at a small selection of the following exposures: food items, energy-yielding nutrients, vitamins, and other factors. Furthermore, the review by Wirdefeldt et al. (2011) found 14 case-control and five prospective studies on alcohol and PD, and three case-control and four prospective studies on physical activity and PD. Regarding coffee consumption and PD, one meta-analysis included 17 cross-sectional or case-control studies and nine prospective studies (see Costa et al. 2010).

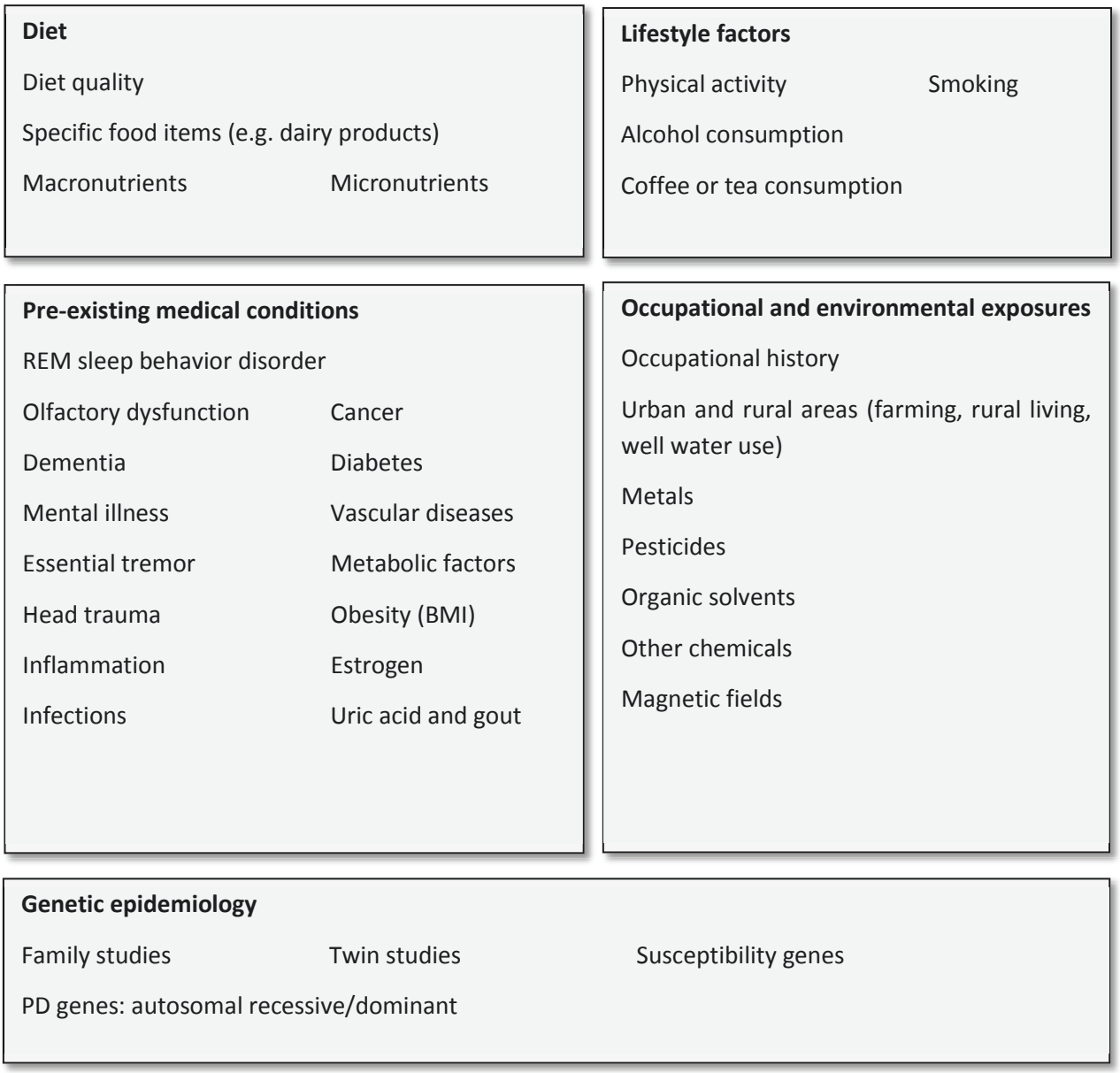

Figure 1. Areas of epidemiologic research conducted on PD. Abbreviations: PD, Parkinson's disease; REM, rapid eye movement; BMI, body mass index. Adapted from following reviews: Wirdefeldt et al. 2011; and de Lau and Breteler 2006a.

Regarding metabolic factors and PD, the review by Wirdefeldt et al. (2011) found 10 case-control and four prospective studies on diabetes and PD, and 11 case-control and three prospective studies on hypertension or blood pressure and PD. Furthermore, the review identified six case-control and one prospective studies on heart disease or stroke and PD, as well as three case-control and four prospective studies on serum cholesterol levels and PD.

Cross-sectional or case-control studies are not an optimal design for etiologic studies, as retrospective exposure measurements are extremely prone to bias, for example when addressing nutritional exposure occurring many years in the past (Willett 1998). A focus on prospective studies in the future is clearly needed. Furthermore, the studies vary greatly in methodological aspects, such as case ascertainment and inclusion of confounding factors. Thus, the following review attempts to acknowledge these aspects too.

2.2.2 Inclusion criteria for the literature review

The literature review of this thesis covers only those prospective studies examining the associations between PD risk and those exposures stated in the aims of this study (diet quality; food groups; physical activity; alcohol consumption; smoking; obesity; blood pressure; blood concentration of triglycerides, HDL cholesterol, total cholesterol, and glucose; metabolic syndrome). However, if the literature on a specific topic was limited or lacking prospective studies, studies employing other designs are briefly mentioned. Furthermore, the results of a few systematic reviews and meta-analyses are mentioned to complement the overview.

All relevant prospective studies have been included, without any limitations on the size of the study, type of the publication, or publication or baseline year. An example of search protocol for the literature review is presented in Appendix Table 1. In addition to the literature search, the references of included studies and a few recent review articles were also searched. In this review, the term 'prospective study' refers to cohort designs, nested case-control designs, or other longitudinal designs.

One reason for restricting the review to prospective studies is that the focus of the current study is not on PD patients, but in predicting future PD. Furthermore, a case-control design is not optimal for studying etiologic clues. Retrospective studies were excluded because they are prone to bias, especially when addressing exposure occurring many years in the past.

The results of the studies mentioned in the following chapters and tables are from multivariate models that adjusted for at least smoking, unless otherwise stated. Smoking is a strong confounding factor both predicting PD and associating with most of the exposures examined.

2.2.3 Diet and the risk of PD

As the aim of this study was to assess the diet as a whole, this review focuses on studies of diet quality, as well as food groups and items that are components of the diet quality indices. However, a brief chapter on nutrients is also included to support the interpretation of the results by giving background on potential biological mechanisms underlying the associations. Furthermore, coffee and alcohol consumption have been reviewed separately in chapter 2.2.4.

A wide variety of nutritional exposures have been studied for their association with PD, e.g. food items, macronutrients (such as protein, fat, and carbohydrates), and micronutrients (e.g. vitamins, minerals, and phytochemicals) (see Ishihara and Brayne 2005). However, the number of prospective studies on individual dietary factors is limited.

There were seven publications on prospective studies of specific food groups or items and the risk of PD. These studies and their results are described in Tables 2 and 3. Five of these studies were from the United States, as well as one from Greece and one from China. Studies with more than 100 PD cases were all from the United States. Most of the studies measured dietary intake with food frequency questionnaires, while two reported using 24-hour recall (Table 2).

Diet quality

Diet quality can be studied with dietary indices reflecting adherence to a predefined dietary habit, with data-driven approaches (principal components analysis and cluster analysis) describing actual intake patterns in the population, or with reduced rank regression looking for associations between food intake

and the outcomes (see Tucker 2010). In this study, we used the dietary index method to describe the diet quality.

There is only one previous prospective study on diet quality and PD risk. This large cohort study (n=508 PD cases) pooling together the Nurses' Health Study and the Health Professionals Follow-Up Study assessed participant's dietary intake with a food frequency questionnaire (131 items for men and 116 for women) (Gao et al. 2007). Diet quality was measured with the Alternate Healthy Eating Index (AHEI) and with the alternate Mediterranean Diet Score (aMED). Both indices had an inverse association with PD risk (*P* for trend for AHEI 0.01, and for aMED 0.07). The risk of PD was 30% lower for those in the highest quintile of the AHEI score compared with the lowest quintile. The corresponding reduction in risk for aMED was 25%. These results indicate that a diet characterized by a high intake of fruits, vegetables, legumes, whole grains, nuts, fish, and poultry and a low intake of saturated fat and a moderate intake of alcohol may protect against PD. This finding was supported by a case-control study from the United States where PD patients (n=257) were found to be less likely to adhere to the Mediterranean-type diet than controls (Alcalay et al. 2012). The study assessed the current diet (i.e. from the preceding year) with a 61-item food frequency questionnaire.

In addition, Gao et al. (2007) conducted a principal components analysis identifying two dietary patterns, prudent and Western. The prudent score, characterized by high intakes of fruit, vegetables, and fish, was inversely associated with PD risk (*P* for trend 0.04), but the Western pattern was not. Furthermore, a case-control study from Japan with 249 PD patients identified three dietary patterns (Healthy, Western, and Light) by factor analysis (Okubo et al. 2012). The Healthy pattern, consisting of high intakes of vegetables, fruits, and fish, was inversely associated with PD risk. The study assessed the current diet (i.e. from the preceding month) of the PD patients with a dietary history questionnaire of 150 items.

However, it is possible that the dietary habits of the PD patients are a result of the PD status rather than its cause. The non-motor symptoms of PD, such as loss of sense of smell, constipation, and mood and cognitive disorders (see Gaig and Tolosa 2009) are likely to affect individuals' dietary habits. More prospective studies on diet quality and PD risk are urgently needed.

Food groups or items

In general, no association between any individual food groups or items and the risk of PD were found in most of the prospective studies (Table 3). The few exceptions were consumption of milk products, nuts, and legumes.

Four studies found a positive association between consumption of milk and the risk of PD (Kyrozis et al. 2013; Chen et al. 2007; Park et al. 2005; Chen et al. 2002). Three of the studies were from the United States (Chen et al. 2007; Park et al. 2005; Chen et al. 2002), and one from Greece (Kyrozis et al. 2013). However, two of these studies, large cohorts from the United States (Chen et al. 2007; Chen et al. 2002), analyzed the results separately for men and women and found the positive association between milk product consumption and PD risk in men only. The study by Park et al. (2005) included only men, whereas Kyrozis et al. (2012) did not report men and women separately. Thus the potential gender difference in this association should be examined in future studies.

Furthermore, an inverse association between PD risk and the consumption of nuts (Zhang et al. 2002) and legumes (Morens et al. 1996) has been observed in large cohort studies from the United States. However, there are no other prospective studies to replicate these findings.

Table 2. Description of prospective studies on food groups or items and Parkinson's Disease.

Country/reference, Study design	Study name, Baseline year	Population N/n[a], Gender	Age at baseline		Follow-up years	PD ascertainment	Dietary Assessment		
			Mean	Range			Method	Food items (n)	Time period
USA/ (Morens et al. 1996), NCCS	Honolulu-Asia Aging Study, 1965–1968 (originally called the Honolulu Heart Study)	336/84[b], M	54	45-68	27-30	identified by hospital records, records of local neurologists, death certificates, or re-screening of the cohort	a part of 24 h dietary recall	-	24 h[c]
							FFQ (interviewed)	26	NR
USA/ (Park et al. 2005), CS	Honolulu-Asia Aging Study, 1965–1968	7,504/128, M	54	45–68	30	SAA	a part of 24 h dietary recall	-	24 h
USA/ (Chen et al. (2002), CS	Nurses' Health Study, 1980	88,563/184, F	-	30–55	18	identified by self-report or death certificate, ascertained by treating physician or reviewing medical records	FFQ	61	12 mo
USA/ (Zhang et al. 2002), CS	Nurses' Health Study, 1984	76,890/161, F	-	30–55	14	SAA	FFQ	61	12 mo
USA/ (Chen et al. (2002), CS	Health Professionals Follow-up Study, 1986	47,331/210, M	-	40–75	12	identified by self-report or death certificate, ascertained by treating physician or reviewing medical records	FFQ	131	12 mo
USA/ (Zhang et al. 2002), CS	Health Professionals Follow-up Study, 1986	47,331/210, M	-	40–75	12	SAA	FFQ	131	12 mo
China/ (Ma et al. 2006), NCCS	Nutritional Intervention Trial, 1986	340/85, F and M	-	40–69	14	neurological examination in follow-up screening	interview using a structured questionnaire	NR	12 mo
USA/ (Chen et al. 2007), CS	Cancer Prevention Study II Nutrition Cohort, 1992–1993	130,864/388, F and M	-	50–74	10	self-report, ascertained by treating physician or reviewing medical records	FFQ	68	12 mo
Greece/ (Kyrozis et al. 2012), CS	EPIC-Greece, 1993–1999	25,407/88, F and M	-	20–86	mean 8.45	self-reported, ascertained with a telephone interview of the patients themselves	FFQ	150	12 mo

Abbreviations: NCCS, nested case-control study; CS, cohort study; M, male; F, female; SAA, same as above; FFQ, food frequency questionnaire; NR, not reported; h, hour; mo, month.

[a] N/n = total population/PD cases

[b] matched by year of birth ±2 years

[c] excluded those who reported atypical 24-hour intakes

Table 3. Summary of prospective study findings on food groups or items and the risk of Parkinson's disease[a].

Food groups or item	No association	Increased risk (positive association)	Decreased risk (inverse association)
Grains (or cereals)	NHS, Chen et al. 2002 HPFS, Chen et al. 2002 EPIC-G, Kyrozis et al. 2012	NR	NR
- Rye	NR	NR	NR
- Wheat	NR	NR	NR
- Whole grains	NR	NR	NR
Vegetables	NHS, Chen et al. 2002 HPFS, Chen et al. 2002 EPIC-G, Kyrozis et al. 2012 NIT, Ma et al. 2006	NR	NR
- Legumes and nuts	NR	NR	Nuts: NHS, Zhang et al. 2002 HPFS, Zhang et al. 2002 Legumes: HAAS, Morens et al. 1996
- Potato	NR	NR	NR
- Roots	NR	NR	NR
Fruits and berries	NR	NR	NR
- Fruits, fresh	NHS, Chen et al. 2002 HPFS, Chen et al. 2002 (NR whether fresh or canned) NIT, Ma et al. 2006	NR	NR
- Berries	NR	NR	NR
Margarines	NR	NR	NR
Oils, mayonnaise	NHS, Zhang et al. 2002 HPFS, Zhang et al. 2002 HAAS, Morens et al. 1996	NR	NR
Butter	HPFS, Chen et al. 2002	NR	NR
Milk and milk products	NHS, Chen et al. 2002	HPFS, Chen et al. 2002 CPS-II, Chen et al. 2007 EPIC-G, Kyrozis et al. 2012	NR
- Milk	NR	HPFS, Chen et al. 2002 HAAS, Park et al. 2005 CPS-II, Chen et al. 2007 EPIC-G, Kyrozis et al. 2012	NR
- Cheese	CPS-II, Chen et al. 2007 EPIC-G, Kyrozis et al. 2012	HPFS, Chen et al. 2002	NR
- Fermented milk products	CPS-II, Chen et al. 2007 EPIC-G, Kyrozis et al. 2012	HPFS, Chen et al. 2002	NR
Meat and meat products (i.e. Total meat)	NHS, Chen et al. 2002 HPFS, Chen et al. 2002 EPIC-G, Kyrozis et al. 2012	NR	NIT, Ma et al. 2006
- Red meat	NHS, Chen et al. 2002 HPFS, Chen et al. 2002	NR	NR
- Processed meat and sausages	NR	NR	NR
- Poultry	NHS, Chen et al. 2002 HPFS, Chen et al. 2002	NR	NR
- Ratio of white meat to red meat	NR	NR	NR
Fish	NHS, Chen et al. 2002 HPFS, Chen et al. 2002 EPIC-G, Kyrozis et al. 2012	NR	NR
Eggs	NIT, Ma et al. 2006	NR	NR
Sugar and sugar rich condiments (or sweets and desserts)	NHS, Chen et al. 2002 HPFS, Chen et al. 2002	NR	NR

Abbreviations: NR, not reported or no previous studies exist; NHS, Nurses' Health Study; HPFS, Health Professionals Follow-up Study; EPIC-G, EPIC-Greece; HAAS, Honolulu-Asia Aging Study; CPS-II, Cancer prevention Study II; NIT, Nutritional Intervention Trial.

[a] the categories in the table are chosen to represent the whole diet

Energy-yielding nutrients

Most of the prospective studies on diet and PD risk have examined the association between individual nutrients and PD risk.

Total protein intake was not associated with PD risk in three of the large cohort studies: the Singapore Chinese Health Study (Tan et al. 2008), the Nurses' Health Study (Chen et al. 2003a), and the Health Professionals Follow-up Study (Chen et al. 2003a). The Cancer Prevention Study II Nutrition Cohort study, however, reported a higher risk of PD for increased total protein intake, and this association was stronger for protein from dairy sources than from non-dairy sources (Chen et al. 2007). For carbohydrates, two cohort studies found no association (Tan et al. 2008; Chen et al. 2003a), but in the Honolulu-Asia Aging Study PD incidence rose significantly with increasing intake both in non-coffee drinkers and never smokers (Abbott et al. 2003).

The Nurses' Health Study and the Health Professionals Follow-up Study reported that the intakes of total fat or major types of fat were not significantly associated with PD risk (Chen et al. 2003a). However, they found that, in men, replacement of polyunsaturated fat with saturated fat was associated with a significantly increased risk. Additionally, the National Institutes of Health-American Association of Retired Persons Diet and Health Study found no association between overall fat intake or other macronutrients and PD risk, but a weak positive association between intake of n-6 polyunsaturated fatty acids and PD risk was observed (Dong et al. 2014). An inverse association between PD incidence and intake of total fat, as well as monounsaturated and polyunsaturated fat, was found in the prospective Rotterdam Study (de Lau et al. 2005a). In accordance, the Greek cohort of the European Prospective Investigation into Cancer and Nutrition (EPIC), EPIC-Greece study, found an inverse association between polyunsaturated fat intake and incident PD (Kyrozis et al. 2013), as did the Honolulu-Asia Aging Study, reporting that the intake of polyunsaturated fats appeared protective against PD in men who never smoked cigarettes (Abbott et al. 2003). While the Singapore Chinese Health Study did not find an inverse association for polyunsaturated fat, an inverse association was found for monounsaturated fat (Tan et al. 2008).

Total energy intake had no association with PD in the four prospective cohort studies (Kyrozis et al. 2013; Chen et al. 2003a; Abbott et al. 2003).

A recent meta-analysis examined macronutrient intakes and the risk of PD (see Wang et al. 2015). The meta-analysis included studies reporting on protein intake (4 prospective studies and 3 case-control studies), carbohydrate intake (4 and 4, respectively), fat intake (7 and 5, respectively), and energy intake (4 and 4, respectively). The meta-analyses concluded that after adjusting for smoking and coffee/caffeine intake, no associations were found between these macronutrients and PD risk, but that higher polyunsaturated fat intake might be inversely associated with PD risk.

Vitamins and other factors

As oxidative stress is one of the hypothesized pathogenic mechanisms in PD, the role of antioxidants has been studied; however, the number of prospective studies is low. The review by Wirdefeldt et al. (2011) reports that three out of four prospective studies found an inverse association between vitamin E intake and PD incidence. Four prospective studies in the review examined vitamin C intake, two vitamin A intake, and one beta-carotenoid intake, but none of them found an association with PD risk. Only one prospective study has examined the association between dietary flavonoids and risk of PD, and the results suggested that total flavonoid intake was inversely associated with PD risk in men but not women (Gao et al. 2012). Furthermore, four prospective studies have assessed the relationship between serum uric acid levels and

PD, all reporting an inverse association between baseline serum uric acid and PD (see Wirdefeldt et al. 2011).

Since homocysteine has been hypothesized to have neurotoxic effects, vitamins B6, B12, and folate have been examined in relation to PD. According to the review by Wirdefeldt et al. (2011), the three prospective studies conducted on those vitamins did not find any particular associations with PD risk, except one which showed an inverse association between the intake of vitamin B6 and risk of PD.

There is only one known prospective study reporting on blood levels of vitamin D; the Mini-Finland Health Survey found an inverse association between serum 25-hydroxy vitamin D level and PD incidence (Knekt et al. 2010). On the other hand, a large cohort study from the United States found that total dietary intake of vitamin D was unrelated to PD risk, but that vitamin D intake from dairy products was associated with a higher risk of PD (Chen et al. 2007). Another cohort study from Greece found no association between dietary vitamin D intake and PD risk (Kyrozis et al. 2013).

The prospective studies examining the associations between minerals and PD risk are even more scarce than for other nutrients. The Nurses' Health Study and the Health Professionals Follow-up Study reported that calcium supplements were not related to PD risk (Chen et al. 2002). However, after stratification of participants by levels of vitamin intake, non-heme iron was associated with an increased risk in those who had low vitamin C intake (Logroscino et al. 2008).

Summary on dietary factors

There are only ten prospective datasets that include dietary measurements at baseline as well as follow-up information on PD. The studies reported a selected set of varying nutritional factors, most focusing on reporting specific nutrients, while some reported on specific food items. Prospective studies are particularly lacking for diet quality, as well as for different types of items within major food groups (Table 3).

The majority of the previous studies, based on this review and the one by Ishihara and Brayne (2005), did not find significant associations between nutritional factors and PD. Some associations were found in case-control studies (see Ishihara and Brayne 2005), but could not be replicated in cohort studies.

Furthermore, it should be noted that the categorization of food items into larger food groups may differ between studies. These differences may have an impact on the results, thus being one contributor to the discrepancies in the literature, especially between prospective and case-control studies. Furthermore, prospective studies more often used food frequency questionnaires with a one year reference period, whereas most of the case-control studies used undefined questionnaires or interviews with different reference periods. Accordingly, these different methods produce varying results.

Overall, dietary factors do not seem to play a major role in PD, although a few promising results have been obtained (e.g. associations with vitamin E and polyunsaturated fat intake, as well as urate concentration). However, more prospective studies are needed.

2.2.4 Lifestyle and the risk of PD

Leisure-time physical activity

Physical activity has been suggested to be one of the most important protective factors against chronic diseases like cardiovascular disease, diabetes, and some cancers (see Reiner et al. 2013). There is also evidence that exercise may protect against some neurodegenerative diseases like Alzheimer's disease (see Han and Han 2014). Furthermore, the association between physical activity and PD risk has increasingly gained attention over the past few years.

The prospective studies regarding physical activity and PD conducted thus far are described in Tables 4 and 5. Additionally, a few case-control studies have been carried out (see Wirdefeldt et al. 2011), though most of those reported either a non-significantly reduced risk of PD or no association, with rather similar results in both genders. However, the largest cohort study, with 413 PD cases and 141,339 subjects in total, from the United States (Thacker et al. 2008), reported a significant inverse association between leisure-time physical activity and PD risk, suggesting that the association was due to moderate to vigorous rather than light activity. Furthermore, the most recent cohort study, from Sweden (including 43,368 subjects, 286 with incident PD), reported an inverse association between PD risk and overall physical activity (household, commuting activity, and leisure-time exercise together), but not leisure-time exercise alone (Yang et al. 2015).

A meta-analysis of four prospective studies showed a pooled hazard ratio of 0.66 (95% confidence interval (CI) 0.57–0.78) for highest versus lowest physical activity level (Yang et al. 2015). However, the study did not report the classification of the physical activity levels, or type of physical activity, for the pooled result. Moreover, the analysis did not include the findings from four studies reporting no association or a non-significant decreased risk of PD (Kyrozis et al. 2013; Tan et al. 2008; Paganini-Hill 2001; Sasco et al. 1992). The authors stated that the reason for this exclusion was to analyze only studies reporting gender-specific information.

In summary, several observational studies on PD risk and physical activity point toward a weak inverse association, but the type of protective physical activity remains unknown.

Smoking

Smoking is one of the most studied risk factors for PD. An inverse association between smoking and PD was first reported in a study from 1959 examining death rates and tobacco consumption (Dorn 1959). However, accuracy and underreporting of PD diagnoses remain a concern if PD ascertainment is made based solely on death certificates.

The results from previous cohort studies, described in Tables 6 and 7, are consistent in reporting a strong inverse association between smoking and PD. Meta-analyses have also found similar results (see Ritz et al. 2007; see Allam et al. 2004; see Hernan et al. 2002; see Sugita et al. 2001). The meta-analysis by Hernan et al. (2002) included four cohort studies and 44 case-control studies from 20 countries, and reported a pooled relative risk (RR) of 0.39 (95% CI 0.32–0.47) for current vs. never smokers, 0.59 (95% CI 0.54–0.63) for ever vs. never smokers, and 0.80 (95% CI 0.69–0.83) for past vs. never smokers.

Furthermore, the meta-analysis by Ritz et al. (2007) (3 cohort and 8 case-control studies, all from the United States) focused on the intensity, duration, and types of tobacco use, suggesting a dose-dependent reduction in PD risk with cigarette smoking and potentially other types of tobacco use. They also found

that the shorter the time since smoking cessation, the lower the risk of PD. This meta-analysis did not find any effect modification by sex or education.

The inverse association between smoking and PD risk could be explained by different biases, such as information bias, difficulties in diagnosing PD, competing causes of death, reverse causation (if PD patients were less prone to smoke), or confounding not accounted for in the studies (e.g. genetic factors). However, twin studies controlling for both genetic and shared early environmental factors have reported an inverse association between smoking and PD, thus implying that confounding by genetic factors is unlikely (Wirdefeldt et al. 2005; Tanner et al. 2002).

One suggestion for why PD patients would be less prone to smoke is the premorbid personality of PD patients, including reduced sensation-seeking traits, which in turn relates to abstaining from addiction-related habits (Evans et al. 2006). Patients with PD show reduced scores on impulsive sensation-seeking inventories and are less likely to engage in sensation-seeking behavior (see Menza 2000). Whether this type of personality shares a genetic background with PD pathogenesis, or is an early preclinical symptom of the disease, is unknown. However, a meta-analysis of 3 cohort and 8 case-control studies reporting that even subjects who stopped smoking 15-25 years before the study baseline had a decreased risk of PD compared to never smokers (see Ritz et al. 2007), argues against the above mentioned hypothesis of premorbid personality as an early symptom of the disease. Therefore, an alternative hypothesis to explain the inverse association between smoking and PD is that patients in the prodromal phase of PD might have a decreased "responsiveness" to nicotine resulting in less long-term use and addiction (Ritz et al. 2014).

One cohort study examining the association between parental smoking and PD risk (to account for a non-genetic unknown confounding factor) found an inverse association (O'Reilly et al. 2009). The authors concluded that if the inverse association between smoking and PD were due to confounding by an environmental factor or were the result of reverse causation, it is unlikely that parental smoking would predict PD. Finally, although causality has been debated, the inverse association between smoking and PD risk has been found across different study designs and populations around the world, while taking into account different effect-modifying factors or potential confounding, and indicates a clear dose-response relationship (see Wirdefeldt et al. 2011).

In summary, there seems to be strong epidemiological evidence that smokers have a lower risk of PD. However, the biological mechanism underlying this potentially protective effect has not been identified, and there is still doubt that the association is due to reverse causation or some unknown confounding factor.

Alcohol consumption

There are suggestions of an inverse association between addiction-related habits (e.g. smoking and coffee consumption) and PD risk, due to the reduced sensation-seeking traits of PD patients (Evans et al. 2006). Thus, association between alcohol consumption and PD risk has also been examined.

The prospective studies conducted previously, described in Tables 8 and 9, report mostly no association between alcohol intake and PD risk. In addition, the results from case-control studies were rather similar (see Wirdefeldt et al. 2011). However, summarizing the results of these studies is difficult, as exposure variables were estimated differently, from calculation of the total amount of alcohol consumed (as ethanol, or as number of drinks per month or week) to simple dichotomous 'ever vs. never' variables. Furthermore, studies utilizing only dichotomous variables on alcohol consumption ignore the dose effect. Additionally, few studies examined consumption levels across specific types of alcohol. Indeed, a large

cohort study from the United States found a statistically significant inverse association between beer consumption (estimated as number of drinks) and risk of PD (Hernan et al. 2003).

Results from these previous studies show that controlling for confounding factors is important, as many studies found an inverse association in univariate analyses, but after controlling for confounding factors like smoking and coffee consumption the results were no longer statistically significant (see Wirdefeldt et al. 2011). This might imply that the inverse association between alcohol consumption and PD risk found in some case-control studies could be due to residual confounding. On the other hand, smoking could also be an effect-modifying factor, masking the association between alcohol and PD: a Swedish nested case-control study found an inverse association between alcohol consumption and PD risk only among never smokers (odds ratio 0.56, 95% CI 0.39–0.80 for ever vs. never drinkers) (Wirdefeldt et al. 2005).

In summary, the number of prospective studies is limited, though the results point toward no association between alcohol consumption and PD risk. However, the lack of uniformity in reporting alcohol intake as well as inadequate sample sizes and variable PD ascertainment method should be considered when interpreting the results. Converting drink units and portions into grams of ethanol for analysis, as well as measuring different beverage types, would enhance comparability between the studies.

Coffee consumption

Coffee consumption is a dietary habit that has been inversely associated with alcohol consumption and smoking (Sääksjärvi et al. 2008; Hu et al. 2007a; Ascherio et al. 2004). Therefore, it has also been of interest in epidemiological studies on PD.

This review revealed 14 previously conducted prospective studies, described in Tables 10 and 11, although two of them were re-analyses of data that had previously been reported (highlighted with grey in the Table 10: Ross et al. (2000), Ascherio et al. (2003)). Most of the studies found a statistically significant inverse association between coffee consumption or caffeine intake and PD risk. There are observations of an effect modification by gender that could be explained by hormone replacement therapy; a few studies from the United States suggest that coffee or caffeine intake reduces PD risk among those women not using postmenopausal hormones (Palacios et al. 2012b), however, among hormone users, the risk might increase (Ascherio et al. 2004; Ascherio et al. 2003). Additionally, smoking has been found to modify the association between coffee consumption or caffeine intake and risk of PD, but with contrasting results (for women, the association was present in ever smokers, but for men, in never smokers) (Palacios et al. 2012b).

Caffeine from non-coffee sources (e.g. tea, cola beverages, chocolate) has also been inversely associated with PD risk (Ascherio et al. 2001; Ross et al. 2000). In contrast, three prospective studies reported no association between tea intake and PD risk (Kyrozis et al. 2013; Hu et al. 2007a; Paganini-Hill 2001). However, only one study has examined black and green tea separately, finding an inverse association between black tea intake and PD risk (Tan et al. 2008).

There are three meta-analyses of observational studies on self-reported coffee or caffeine exposure and PD risk (see Qi and Li 2014; see Costa et al. 2010; see Hernan et al. 2002). The largest one included 26 studies (7 cohort, 2 nested case-control, 16 case-control, and 1 cross-sectional study) and reported a summary relative risk of 0.76 (95% CI 0.72–0.80) per 300 mg increase in caffeine intake (see Costa et al. 2010). Two of the meta-analyses (see Costa et al. 2010; see Hernan et al. 2002) concluded that caffeine exposure or coffee drinking is associated with a lower risk of PD, while the third one stated that further research is required to confirm the findings (see Qi and Li 2014).

The previously mentioned biases (regarding the association between smoking and PD risk) are also a concern in studies on coffee and PD (see page 24). Indeed, a twin study controlling for both genetic and shared early environmental factors did not find an association between coffee consumption and PD risk (Wirdefeldt et al. 2005). Furthermore, reverse causation is generally thought to be an unlikely bias in a prospective design. However, since PD is a disease with a several decades-long preclinical disease phase (see Gaig and Tolosa 2009), reverse causation remains a concern, as there are suggestions that reduced sensation-seeking traits in preclinical PD patients lead to abstaining from addiction-related habits (Evans et al. 2006). This concern has not adequately been addressed in studies regarding coffee or caffeine exposure and PD risk. Thus, further prospective studies with several decades of follow-up (enabling the exclusion of the first 10–20 years of follow-up), or retrospective information on coffee consumption 10–20 years prior to the study baseline, is needed.

2.2.5 Obesity, metabolic health, and the risk of PD

Metabolic health and obesity are complex conditions which may have adverse health effects. However, little is known about their association with PD risk.

Obesity

Conflicting results on the association between obesity and PD risk have been reported (Tables 12 and 13). In prospective studies, subjects with high BMI (Hu et al. 2006) or increased tricep skinfold thickness (Abbott et al. 2002) have been associated with higher risk of PD. However, one nested case-control study found an inverse association between BMI and PD incidence (Ma et al. 2006). On the other hand, all the other reviewed prospective studies (Vikdahl et al. 2015; Kyrozis et al. 2013; Palacios et al. 2011; Tan et al. 2008; Logroscino et al. 2007; Chen et al. 2004; Paganini-Hill 2001) reported null associations.

This inconsistency could be explained by the preclinical disease stage of PD masking the associations, since PD patients tend to lose weight as the disease progresses, with the process beginning several years before clinical diagnosis (Chen et al. 2003b). The large cohort studies from the United States that did not find an association between BMI and PD risk excluded only the first 3–5 years of follow-up (Palacios et al. 2011; Logroscino et al. 2007; Chen et al. 2004). Moreover, most of the studies evaluated here did not report performing any kind of lag analyses, or excluded less than a year from the beginning of follow-up (Vikdahl et al. 2015; Kyrozis et al. 2013; Tan et al. 2008; Hu et al. 2006; Ma et al. 2006; Abbott et al. 2002; Paganini-Hill 2001).

Further studies should consider the effect of the potential preclinical disease phase that could mask the association between BMI and PD risk with sensitivity analyses regarding the beginning of the follow-up period.

Furthermore, smoking could be an effect-modifying factor, as a large cohort study from the United States (including 164,762 total subjects, 451 with PD) found that higher waist circumference and waist-to-hip ratios were associated with increased PD risk when analyses were restricted to never smokers (Chen et al. 2004).

Blood Pressure or hypertension

There were seven prospective studies on the association between blood pressure or hypertension diagnosis and PD, as described in Tables 14 and 15. Results are conflicting; most of the studies found no

association between blood pressure/hypertension and PD risk, while a few found either a decreased risk (Vikdahl et al. 2015; Paganini-Hill 2001) or increased risk (Qiu et al. 2011). However, it should be noted that three of the studies finding no association were vague in their reporting of methods or analysis results (Tan et al. 2008; Ma et al. 2006; Grandinetti et al. 1994). The studies did not report, for example, the exposure categories compared, or what factors were adjusted for.

Gender might be an effect-modifying factor here, as a Finnish cohort study (including 59,540 total subjects, 794 with PD) reported no association for men but a positive association for women (Qiu et al. 2011).

Blood pressure or hypertension diagnosis have been examined in more than ten case-control studies, as reviewed by Wirdefeldt et al (2011). However, the results from them have also been conflicting (see Wirdefeldt et al. 2011). One reason for the varying results in observational studies could be different methodology, as some studies included measurements on blood pressure while others relied on self-reported information on blood pressure or diagnosed hypertension.

Serum HDL cholesterol and total cholesterol

There are two prospective studies on the association between HDL cholesterol and PD risk as described in Table 14. Neither of the studies found any association with PD risk. It should be, however, noted that the article by Huang et al. (2008) stated only that there was no association between HDL cholesterol and PD risk. For example, they did not report what exposure categories were compared or whether the models were adjusted or not.

Similarly, the case-control studies from Italy and the United States did not found association between HDL cholesterol levels and PD (Cereda et al. 2012; Huang et al. 2007). Further prospective studies are, however, needed.

Serum HDL cholesterol was included in the present study since it is one of the criteria of metabolic syndrome. However, serum total cholesterol has also gained interest in previous studies. Thus, serum total cholesterol was also included in this study. Briefly, two cohort studies reported reduced (Simon et al. 2007; de Lau et al. 2006b) and one increased (Hu et al. 2008) PD risk for increasing total cholesterol levels.

Serum triglycerides and glucose

There are no previous cohort studies examining the association between serum triglycerides and PD risk, or between blood glucose levels and PD risk. One nested case-control study from Sweden, however, included these factors (see Table 15). The study comprised 84 PD cases and 336 controls, and had a rather short follow-up time (2–8 years) (Vikdahl et al. 2015). There appeared to be an inverse association between serum triglycerides and PD risk, but after adjustments in the multivariate model, including smoking, the result was borderline significant. However, the results from the study by Vikdahl et al. (2014) are hard to interpret, and more studies are needed.

There are three previous case-control studies on PD and serum triglyceride concentration, all reporting that cases had a significantly lower serum triglyceride level than controls (Wei et al. 2013; Cereda et al. 2012; Scigliano et al. 2006). Two of the studies also reported lower levels of fasting blood glucose in PD cases compared to controls (Cereda et al. 2012; Scigliano et al. 2006).

Metabolic syndrome

There are no previous prospective studies examining the association between metabolic syndrome and PD risk. One case-control study from Italy (80 PD cases and 80 controls) found a similar prevalence of metabolic syndrome among cases and controls (Cereda et al. 2012). That study used The National Cholesterol Education Program's Adult Treatment Panel III criteria (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) 2001) which are otherwise the same as those used in the present study, but did not include information on antihypertensive drug treatment and used a higher cut-off point for glucose (6.1 mmol/l, whereas 5.6 mmol/l was used in the present study). Furthermore, the study had information on waist circumference, whereas the present study used information on BMI.

Table 4. Physical activity and Parkinson's disease: Cohort studies.

Country/ reference	Study name, baseline year	Population N/n[a], gender	Follow-up years	PD ascertainment	Measuring method of exposure	Exposure (unit)	Exposure categories compared	Adjusted result RR (95%CI)	*P* for trend	Adjustments
USA/ (Chen et al. 2005)	Nurses' Health Study, 1986	77,254 /135, F	12	self-report, ascertained by treating physician	Q	leisure-time physical activity, walking, and stair climbing together (MET-h/week)	highest vs. lowest quintile	1.3 (0.7–2.3)	0.97	age, smoking, alcohol, caffeine, energy intake, lactose intake, BMI
						vigorous activity (MET-h/week)	highest vs. lowest quintile	1.0 (0.6–1.7)	0.7	
USA/ (Chen et al. 2005)	Health Professionals Follow-Up Study, 1986	48,574 /252, M	14	self-report, ascertained by treating physician	Q	total leisure-time physical activity + walking, stair climbing (MET-h/week)	highest vs. lowest quintile	0.7 (0.5–1.1)	0.007	age, smoking, alcohol, caffeine, energy intake, lactose intake, BMI
						vigorous activity (MET-h/week)	highest vs. lowest quintile	0.5 (0.3–0.9)	0.004	
USA/ (Logroscino et al. 2006)	Harvard Alumni Health Study, 1988	10,714 /101, M	5 or 9[b]	self-report or death certificates	Q	leisure-time physical activity + walking, stair climbing (kcal expended on physical activity/week)	≥3000 vs. <1000	0.63 (0.36–1.12)	0.12	age, smoking, alcohol, coffee, tea, history of CVD or cancer
Singapore/ (Tan et al. 2008)	Singapore Chinese Health Study, 1993–1998	63,257 /157, F and M	12	self-report or hospital discharge database or PD registry, ascertained by reviewing medical records	interview with a structured Q	physical activity (NR)	NR	NR (just stated: NS)	NR	NR

Table 4. (continued)

Country/ reference	Study name, baseline year	Population N/n[a], gender	Follow-up years	PD ascertainment	Measuring method of exposure	Exposure (unit)	Exposure categories compared	Adjusted result RR (95%CI)	*P* for trend	Adjustments
USA/ (Thacker et al. 2008)	Cancer Prevention Study II, 1992	141,339 /413, F and M[c]	9	self-report, ascertained by treating physician or reviewing medical records	Q	total leisure-time physical activity (MET-h/week)	≥23 vs. no activity	0.8 (0.6–1.2)	0.07	age, education, smoking, years since quitting smoking, alcohol, caffeinated coffee, caloric intake, dairy intake, BMI, pesticide exposure, ibuprofen use
						moderate to vigorous leisure-time activity (MET-h/week)	≥16 vs. no or light activity	0.6 (0.4–1.0)	0.02	
Greece/ (Kyrozis et al. 2013)	EPIC-Greece, 1993–1999	25,407/88, F and M	mean 8.45	self-report, ascertained with self-reported telephone interview	Q	overall activity, occupational and leisure-time	1 MET-h increment	0.95 (0.90–1.00)	0.06	age, sex, marital status, education, farming, smoking, coffee with caffeine, energy intake, BMI
Sweden/ (Yang et al. 2015)	Swedish National March Cohort, NR	43,368 /286, F and M	mean 12.6	any diagnosis of PD in national patient register	Q	household + commuting activity + leisure-time exercise (MET-h/day)	highest vs. lowest tertile	0.72 (0.53–0.99)	0.04	attained age as timescale, adjusting for sex, education, smoking, alcohol, coffee, BMI
						leisure-time exercise (MET-h/day)	highest vs. lowest tertile	0.86 (0.62–1.19)	0.36	
Longitudinal								**OR (95%CI)**		
USA/ (Xu et al. 2010)	NIH-AARP Diet and Health Study, 1996–1997	212,934 /767, F and M	Follow-up survey 2004–2006, PD diagnosed after year 2000	self-report, ascertained by treating neurologist or reviewing medical records	Q	moderate to vigorous activities, work + home + leisure-time (h/week of total activity)	>7 vs. never	0.65 (0.51–0.83)	0.0001	age, sex, race, education, smoking, coffee

Abbreviations: PD, Parkinson's disease; RR, relative risk; CI, confidence interval; F, female; M, male; Q, questionnaire; MET-h, metabolic equivalent task hour, NR, not reported; NS, non-significant; BMI, body mass index; CVD, cardiovascular disease; OR, odds ratio.

[a] Total population/PD cases

[b] Follow-up was 5 years if PD ascertainment was based on self-report from questionnaire, and 9 years if based on information from death certificates

[c] Gender-specific RRs were pooled together

Table 5. Physical activity and Parkinson's disease: Nested case-control studies.

Country/ reference	Study name, baseline year	Population N/n[a], gender	Follow-up years	PD ascertainment	Measuring method of exposure	Exposure (unit)	Exposure categories compared	Adjusted result OR (95% CI)	*P* for trend	Matching	Adjustments
USA/ (Sasco et al. 1992)	Harvard College and University of Pennsylvania attendees, 1916–1950	548/137, M	62 or less, depending on baseline year	self-report or death certificates, ascertained by treating physician	Q	all physical activity in adulthood (energy expenditure kJ/week)	≥13,377 vs. ≤2,100	1.2 (0.56–2.6)	0.92	university, graduation year, age	smoking, weight, diastolic blood pressure, measles
						climbing stairs and walking in adulthood (energy expenditure kJ/week)	≥4,826 vs. ≤2,100	0.88 (0.48–1.6)	0.72		
						any physical activity when young	any vs. none	0.74 (0.31–1.7)			
USA/ (Paganini-Hill 2001)	Leisure World Cohort Study, 1981–1985	2,320/395, F and M	18	hospital discharge database or death certificates, or self-report	Q	exercise	NR	NR (just stated: NS)	NR	sex, birth date, vital status; if dead, death date	NR
Sweden/ (Vikdahl et al. 2014)	Northern Sweden Health and Disease Study, 1986–2009	336/84, F and M	2–8	clinical examination by a neurologist, confirmed by another specialist	Q	leisure-time physical activity	recreational activity vs. inactive	F: 4.30 (1.09–17.02) M: 1.34 (0.47–3.85)	0.04 0.58	sex, age, year of health survey, subcohort, geographic area	age, smoking, BMI
							high activity vs. inactive	F: 1.56 (0.28–8.71) M: 1.45 (0.43–4.83)	0.62 0.55		

Abbreviations: PD, Parkinson's disease; OR, odds ratio; CI, confidence interval; F, female; M, male; Q, questionnaire; NR, not reported; NS, non-significant; BMI, body mass index.

[a] Controls/PD cases

Table 6. Smoking and Parkinson's disease: Cohort studies.

Country/ reference	Study name, baseline year	Population N/n[a], gender	Follow-up years	PD ascertainment	Measuring method of exposure	Exposure (unit)	Exposure categories compared	Adjusted result RR (95% CI)	*P* for trend	Adjustments
USA/ (Grandinetti et al. 1994)	Honolulu-Asia Aging Study (originally Honolulu Heart Study), 1965	8,006/58, M	26	hospital records, death certificates, or records of local neurologists	Q	smoking	ever vs. never	0.44 (0.26–0.75)	NR	age, coffee, alcohol
Netherlands/ (Willems-Giesbergen et al. 2000)	Rotterdam Study, 1990–1993	5,289/53, F and M	average 6.07	PD diagnosed by neurologist at the follow-up examination	interview	smoking	ever vs. never	0.54 (0.29–1.00)	NR	age, sex
USA/ (Hernan et al. 2001)	Nurses' Health Study, 1976	121,700 /153, F	20	self-report, ascertained by treating physician or reviewing medical records	Q	smoking	current vs. never	0.4 (0.2–0.7)	NR	age
USA/ (Hernan et al. 2001)	Health Professionals Follow-up Study, 1986	51,529 /146, M	10	self-report, ascertained by treating physician or reviewing medical records	Q	smoking	current vs. never	0.3 (0.1–0.8)	NR	age
USA/ (Thacker et al. 2007)	Cancer Prevention Study II Nutrition Cohort, 1992	79,977 /142, F; 63,348 /263, M	10	self-report, ascertained by treating physician or reviewing medical records	Q	smoking	current vs. never	0.27 (0.13–0.56)		age[b]
							cigarettes per day		0.009	
Singapore/ (Tan et al. 2008)	Singapore Chinese Health Study, 1993–1998	63,257 /157, F and M	12	self-report or hospital discharge database or PD registry, ascertained by reviewing medical records	interview with a structured Q	smoking	current vs. never	0.29 (0.16–0.52)		age, sex, education, year of interview, dialect
							age at starting to smoke		<0.001	

Table 6. (continued)

Country/ reference	Study name, baseline year	Population N/n[a], gender	Follow-up years	PD ascertainment	Measuring method of exposure	Exposure (unit)	Exposure categories compared	Adjusted result RR (95% CI)	*P* for trend	Adjustments
USA/ (O'Reilly et al. 2009)	Nurses' Health Study, 1976; Health Professionals Follow-up Study, 1986	92,921/287, F; 30,668/168, M	26 18	self-report, ascertained by treating physician or reviewing medical records	Q	parental smoking	both parents smoked vs. neither parent smoked	0.73 (0.53–1.00)		age
							NR, presumably pack years		0.04	
Greece/ (Kyrozis et al. 2013)	EPIC-Greece, 1993–1999	25,407 /88, F and M	mean 8.45	self-report, ascertained with self-reported telephone interview	interview	smoking	current vs. never	0.42 (0.18–0.99)		age, sex, marital status, education, farming, physical activity, coffee, energy intake, BMI
Longitudinal								**OR (95% CI)**		
USA/ (Chen et al. 2010)	NIH-AARP Diet and Health Study, 1995–1996	305,468 /1,662, F and M	a follow-up survey 2004–2006, PD diagnosed after year 1995	self-report, ascertained by treating neurologist or reviewing medical records	Q	smoking	past smoking vs. never	0.78 (0.70–0.86)		age, sex, race, caffeine intake
							current vs. never	0.56 (0.45–0.70)		
							pack-years of smoking		<0.001	

Abbreviations: PD, Parkinson's disease; RR, relative risk; CI, confidence interval; F, female; M, male; Q, questionnaire; NR, not reported; NSAI, non-steroidal anti-inflammatory; OR, odds ratio; BMI, body mass index; NIH-AARP, National Institutes of Health-American Association of Retired Persons.

[a] Total population/PD cases

[b] Adjustment for race, education, physical activity, alcohol, coffee, supplementary vitamin intake, BMI, NSAI drug use, pesticide exposure did not alter the result

Table 7. Smoking and Parkinson's disease: Nested case-control studies.

Country/ reference	Study name, baseline year	Population N/n[a], gender	Follow-up years	PD ascertainment	Measuring method of exposure	Exposure (unit)	Exposure categories compared	Adjusted result OR (95% CI)	*P* for trend	Matching	Adjustments
USA/ (Sasco and Paffenbarger 1990)	Harvard College and University of Pennsylvania attendees, 1916–1950	317/76, M	62 or less, depending on baseline year	self-report or death certificates, ascertained by treating physician	Q	smoking	current vs. never	0.51 (0.26–1.0)[b]	NR	university, graduation year, age	
USA/ (Paganini-Hill 2001)	Leisure World Cohort Study, 1981–1985	2,320 /395, F and M	18	hospital discharge database or death certificates, or self-report	Q	smoking	current (≥ 1 pack/d) vs. never	0.42 (0.22–0.80)		sex, birth date, vital status; if dead, death date	alcohol, coffee, vitamin C and A intake, blood pressure medication, parity
							NR		0.004[b]		
Sweden/ (Wirdefeldt et al. 2005)	Swedish Twin Registry, 1967 or 1973	2,380 /476, unrelated F and M	NR	inpatient discharge register or death certificates	Q	smoking	current vs. never	0.56 (0.40–0.79)		birth year, sex, year answered the Q. Cases had two sets of controls: unrelated, twin	education, alcohol, coffee
							cigarette equivalents		0.010		
		415 same-sex twins					current vs. never	twins: 0.64 (0.37–1.10)			
							cigarette equivalents		0.13		
USA/ (Kamel et al. 2007)	Agricultural Health Study, 1993–1997	53,888 /74, F and M	5	self-report of physician-diagnosed PD	Q	smoking	current vs. never	0.6 (0.2–1.7)	NR	no matching	age, place of residence, type of participant (pesticide applicator or spouse)[c]

Table 7. (continued)

Country/ reference	Study name, baseline year	Population N/n[a], gender	Follow-up years	PD ascertainment	Measuring method of exposure	Exposure (unit)	Exposure categories compared	Adjusted result OR (95% CI)	*P* for trend	Matching	Adjustments
Sweden/ (Vikdahl et al. 2014)	Northern Sweden Health and Disease Study, 1986–2009	336/84, F and M	2–8	clinical examination by neurologist, confirmed by another specialist	Q	smoking	current vs. non-smoker	F: 0.66 (0.24–1.78) M: 0.31 (0.08–1.16)	0.41 0.08	sex, age, year of health survey, subcohort, geographic area	age, physical activity, BMI

Abbreviations: PD, Parkinson's disease; OR, odds ratio; CI, confidence interval; F, female; M, male; Q, questionnaire; NR, not reported; BMI, body mass index.

[a] Controls/PD cases

[b] Unadjusted

[c] 99% of applicators were men, so no further adjustments for sex were made

Table 8. Alcohol consumption and Parkinson's disease: Cohort studies.

Country/ reference	Study name, baseline year	Population N/n[a], gender	Follow-up years	PD ascertainment	Measuring method of exposure	Exposure[b] (unit)	Exposure categories compared	Adjusted result RR (95% CI)	*P* for trend	Adjustments
USA/ (Grandinetti et al. 1994)	Honolulu-Asia Aging Study (originally Honolulu Heart Study), 1965	8,006 /58, M	26	hospital records, death certificates or records of local neurologists	Q	alcohol	NR (interpreted as ever vs. never)	0.76 (0.45–1.28) NR (just stated: NS)	NR	age age, smoking, coffee
Netherlands/ (Willems-Giesbergen et al. 2000)	Rotterdam Study, 1990–1993	5,289 /53, F and M	mean 6.07	PD diagnosed by neurologist at the follow-up examination	FFQ	alcohol	drinkers vs. non-drinkers	0.61 (0.32–1.17)	NR	age, sex, smoking
USA/ (Hernan et al. 2003)	Nurses' Health Study, 1980; Health Professionals Follow-up Study, 1986	88,722 /167, F; 47,367 /248, M	19 15	self-report, ascertained by treating physician or reviewing medical records	Q	ethanol (g/d)	30+ vs. 0	0.7 (0.5–1.2)[c]	0.45	age, smoking, caffeine
						beer (no. of drinks)	≥1/week vs. <1/month	0.7 (0.5–0.9)[c]	0.03	
						wine (no. of drinks)	≥5/week vs. <1/month	1.1 (0.8–1.7)[c]	0.46	
						liquor (no. of drinks)	≥5/week vs. <1/month	1.1 (0.8–1.6)[c]	0.42	
Singapore/ (Tan et al. 2008)	Singapore Chinese Health Study, 1993–1998	63,257 /157, F and M	mean 7	self-report or hospital discharge database or PD registry, ascertained by reviewing medical records	interview with structured Q	ethanol (g/d)	at least weekly drinkers vs. none or less than weekly	0.60 (0.31–1.16)	NR	age, year of interview, sex, dialect, education, smoking, caffeine and black tea consumption

Table 8. (continued)

Country/ reference	Study name, baseline year	Population N/n[a], gender	Follow-up years	PD ascertainment	Measuring method of exposure	Exposure[b] (unit)	Exposure categories compared	Adjusted result RR (95% CI)	*P* for trend	Adjustments
USA/ (Palacios et al. 2012a)	Cancer Prevention Study II Nutrition Cohort, 1992–1993	74,121 /216, F; 58,388 /389, M	10, 12 or 14	self-report, ascertained by treating physician or reviewing medical records	FFQ	ethanol (g/d)	F: 15+ vs. 0	0.77 (0.41–1.45)	0.87	age, smoking, coffee
							M: 30+ vs. 0	1.29 (0.90–1.86)	0.40	
						ethanol from beer (g/d)	10g/d increase	1.01 (0.99–1.03)[d]	NR	
						ethanol from wine (g/d)		1.02 (0.98–1.05)[d]	NR	
						ethanol from liquor (g/d)		0.99 (0.96–1.02)[d]	NR	
Greece/ (Kyrozis et al. 2013)	EPIC-Greece, 1993–1999	25,407/88, F and M	mean 8.45	self-report, ascertained with self-reported telephone interview	interview	alcohol (g/d)	100g increment	0.88 (0.74–1.05)	0.16	age, sex
Longitudinal								**OR (95%CI)**		
USA/ (Liu et al. 2013)	NIH-AARP Diet and Health Study, 1995–1996	306,895 /1,113, F and M	NR[e]	self-report, ascertained by treating neurologist or reviewing medical records	FFQ	alcohol (drinks/d)	≥5 vs. none	0.92 (0.66–1.28)	0.63	age, sex, race, marital status, education, physical activity, smoking, caffeine, self-evaluated health status
						beer (drinks/d)	≥2 vs. none	0.86 (0.60–1.21)[f]	0.86	
						wine (drinks/d)	≥2 vs. none	1.31 (0.89–1.94)[f]	0.66	
						liquor (drinks/d)	≥2 vs. none	1.35 (1.02–1.80)[f]	0.08	
USA/ (Kamel et al. 2007)	Agricultural Health Study, 1993–1997	52,945 /71, F and M	5	self-report of physician-diagnosed PD	Q	alcohol (drinks/month)	≥31 vs. non-drinker	1.3 (0.5–3.3)	NR	age, place of residence, type of participant (pesticide applicator or spouse)[g]

Abbreviations: PD, Parkinson's disease; RR, relative risk; CI, confidence interval; F, female; M, male; Q, questionnaire; NR, not reported; NS, non-significant; FFQ, food frequency questionnaire; OR, odds ratio; NIH-AARP, National Institutes of Health-American Association of Retired Persons.

[a] Total population/PD cases
[b] If reported as ethanol, it is indicated here as ethanol. Otherwise, studies have presumably calculated exposure as alcoholic drinks together as g/d, or reporting is unclear whether calculated as ethanol or alcoholic drinks.
[c] Results are pooled RRs from the two cohorts
[d] Men and women pooled together
[e] A follow-up survey in 2004–2006 inquiring about PD diagnosed after year 2000
[f] In addition to the factors stated in the “Adjustments” column, the individual types of alcoholic beverages were adjusted for simultaneously
[g] 99% of applicators were men, so no further adjustments for sex was made

Table 9. Alcohol consumption and Parkinson's disease: Nested case-control studies.

Country/ reference	Study name, baseline year	Population N/n[a], gender	Follow-up years	PD ascertainment	Measuring method of exposure	Exposure (unit)	Exposure categories compared	Adjusted result OR (95% CI)	*P* for trend	Matching	Adjustments
Sweden/ (Wirdefeldt et al. 2005)	Swedish Twin Registry, 1961/67 or 1973	2,380 /476, unrelated F and M	NR	inpatient discharge register or death certificates	Q	alcohol (g/day)	>30g vs. 0	0.66 (0.34–1.29)	0.75	birth year, sex, year of answering the Q	education, smoking, coffee
							ever vs. never	0.74 (0.59–0.93)[b]			
		415 /415 same-sex twins					>30g vs. 0	twins: 0.72 (0.19–2.65)	0.25		
USA/ (Paganini-Hill 2001)	Leisure World Cohort Study, 1981–1985	2,320 /395, F and M	18	hospital discharge database or death certificates, or self-report	Q	alcohol (drinks/day)	≥2 vs. 0	0.77 (0.58–1.03)	0.01[b]	sex, birth date, vital status; if dead, death date	smoking, coffee, vitamin C and A intake, blood pressure medication, parity
						wine (drinks/day)	≥2 vs. 0	0.80 (0.51–1.24)[b]			
						beer (drinks/day)	≥2 vs. 0	0.32 (0.10–1.06)[b]			
						liquor (drinks/day)	≥2 vs. 0	0.75 (0.55–1.01)[b]			
UK/ (Hernan et al. 2004)	General Practice Research Database, 1995–2000	10,123 /1,019, F and M	1–6	GPRD database: PD diagnosis and received ≥2 prescriptions to treat PD during the follow-up	GPRD database: diagnosis of alcoholism or alcohol-related chronic disease	alcoholism	alcoholics vs. non-alcoholics	1.09 (0.67–1.78)		age (within 1 year), sex, start date of the study	the matching factors, smoking
					self-reported drinking	ethanol units (1 unit=10 ml/week)	>50 vs. 0	1.46 (0.69–3.01)	0.71		

Abbreviations: PD, Parkinson's disease; OR, odds ratio; CI, confidence interval; F, female; M, male; Q, questionnaire; NR, not reported; GPRD, General Practice Research Database.

[a] Controls/PD cases

[b] Unadjusted

Table 10. Coffee consumption and Parkinson's disease: Cohort studies[a].

Country/ reference	Study name, baseline year	Population N/n[b], gender	Follow-up years	PD ascertainment	Measuring method of exposure	Exposure (unit)	Exposure categories compared	Adjusted result RR (95% CI)	*P* for trend	Adjustments
USA/ (Grandinetti et al. 1994)	Honolulu-Asia Aging Study (originally Honolulu Heart Study), 1965	8,006/58, M	26	hospital records, death certificates or records of local neurologists	Q	coffee (NR)	NR (presumably regular drinkers vs. non-drinkers)	0.57 (0.32–1.02)	NR	age, smoking, alcohol
USA/ (Ross et al. 2000)	Honolulu-Asia Aging Study (originally Honolulu Heart Study), 1965	8,004/102, M	30	hospital records, death certificates or records of local neurologists	Q	coffee (g/d)	drinkers vs. non-drinkers	0.45 (0.30–0.71)	<0.001	age, smoking
Netherlands/ (Willems-Giesbergen et al. 2000)	Rotterdam Study, 1990–1993	5,289 /53, F and M	mean 6.07	PD diagnosed by neurologist at the follow-up examination	FFQ	coffee (cups/d)	per cup of coffee per day	0.91 (0.77–1.08)	NR	age, sex, smoking
USA/ (Fink et al. 2001)	Framingham Study, NR	6,048 /58, F and M	10	presence of the cardinal features of PD at the biennial examination	Q	caffeine (coffee + tea, estimated as cups of caffeinated coffee/d)	>3 cups/d vs. no caffeine intake	0.77 (0.29–2.04)	NR	age, sex, smoking
USA/ (Ascherio et al. 2001)	Nurses' Health Study, 1980; Health Professionals Follow-up Study, 1986	88,565 /131, F; 47,351 /157, M	16 10	self-report, ascertained by treating physician or reviewing medical records	FFQ	coffee (cups/d)	6+ vs. 0	F: 1.0 (0.5–2.1) M: 0.5 (0.1–2.1)	0.96 0.02	age, smoking, caffeine
USA/ (Ascherio et al. 2003)	Nurses' Health Study, 1980	77,713 /154, F	18	same	FFQ	coffee (cups/d)	4+ vs. 0, stratified by postmenopausal hormone use never vs. ever	never: 0.75 (0.31–1.86) ever: 1.70 (0.81–3.60)	0.06 0.26	age, smoking, alcohol

Table 10. (continued)

Country/ reference	Study name, baseline year	Population N/n[b], gender	Follow-up years	PD ascertainment	Measuring method of exposure	Exposure (unit)	Exposure categories compared	Adjusted result RR (95% CI)	*P* for trend	Adjustments
USA/ (Ascherio et al. 2004)	Cancer Prevention Study II, 1982	238,058 /340, F; 301,164 /909, M	10	death certificates	Q	coffee (cups/d)	6+ vs. 0	F: 0.90 (0.55–1.48)	0.57	age, smoking, alcohol
								M: 0.63 (0.46–0.86)	0.011	
							F: 4+ vs. 0, stratified by postmenopausal hormone use	never: 0.47 (0.27–0.80)	0.11	
							never vs. ever	ever: 1.31 (0.75–2.30)	0.93	
Finland/ (Hu et al. 2007a)	MONICA, 1982, 1987, 1992, 1997	15,042 /98, F; 14,293 /102, M	21 or less, depending on baseline year (mean 12.9)	registry on reimbursement for PD drugs, diagnosed by neurologist	Q	coffee (cups/d)	5+ vs. 0	0.40 (0.23–0.71)	0.005	age, education, study year, physical activity, smoking, alcohol, tea, BMI, systolic blood pressure, cholesterol, history of diabetes
Singapore/ (Tan et al. 2008)	Singapore Chinese Health Study, 1993–1998	63,257 /157, F and M	mean 7	self-report or hospital discharge database or PD registry, ascertained by reviewing medical records	interview with structured Q	caffeine (mg/d)	highest vs. lowest quartile	0.64 (0.40–1.03)	0.016	age, sex, education, year of interview, dialect, smoking
						coffee (cups/d)	2+ vs. 0	0.78 (0.52–1.17)	0.24	

Table 10. (continued)

Country/ reference	Study name, baseline year	Population N/n[b], gender	Follow-up years	PD ascertainment	Measuring method of exposure	Exposure (unit)	Exposure categories compared	Adjusted result RR (95% CI)	*P* for trend	Adjustments
USA/ (Palacios et al. 2012b)	Cancer Prevention Study II Nutrition Cohort, 1999	63,590 /120, F; 48,532 /197, M	2, 4, 6, or 8	self-report, ascertained by treating physician or reviewing medical records	Q	caffeine (mg/d)	highest vs. lowest quintile	F: 0.61 (0.34–1.09) M: 0.43 (0.26–0.71)	0.05 0.002	age, smoking, alcohol
						coffee	>2 cups/d vs. never	F: 0.69 (0.42–1.15) M: 0.54 (0.37–0.80)	0.09 0.0004	
						decaffeinated coffee	>2 cups/d vs. never	F: 0.80 (0.40–1.59) M: 0.81 (0.51–1.27)	0.58 0.68	
Greece/ (Kyrozis et al. 2012)	EPIC-Greece, 1993–1999	25,407 /88, F and M	mean 8.45	self-report, ascertained with self-reported telephone interview	FFQ, interviewed	caffeinated coffee (ml/d)	100 ml increment	0.92 (0.72–1.18)	0.523	age, sex, smoking
Longitudinal								**OR (95% CI)**		
USA/ (Liu et al. 2012)	NIH-AARP Diet and Health Study, 1995–1996	303,880 /1 100, F and M	follow-up survey 2004–2006, PD diagnosed after year 2000	self-report, ascertained by treating neurologist or reviewing medical records	Diet History Questionnaire	caffeine (mg/d)	highest vs. lowest quintile	0.78 (0.64–0.95)	0.004	age, sex, race, physical activity

Abbreviations: PD, Parkinson's disease; RR, relative risk; CI, confidence interval; F, female; M, male; Q, questionnaire; NR, not reported; FFQ, food frequency questionnaire; BMI, body mass index; OR, odds ratio; NIH-AARP, National Institutes of Health-American Association of Retired Persons.

[a] Re-analyses of previously reported data highlighted with grey

[b] Total population/PD cases

Table 11. Coffee consumption and Parkinson's disease: Nested case-control studies.

Country/ reference	Study name, baseline year	Population N/n[a], gender	Follow-up years	PD ascertainment	Measuring method of exposure	Exposure (unit)	Exposure categories compared	Adjusted result OR (95% CI)	*P* for trend	Matching	Adjustments
USA/ (Paganini-Hill 2001)	Leisure World Cohort Study, 1981–1985	2,320 /395, F and M	18	hospital discharge database or death certificates, or self-report	Q	coffee intake (cups/d)	2+ vs. 0	0.71 (0.52–0.95)	0.003[b]	sex, birthdate, vital status; if dead, death date	smoking, alcohol, vitamin C and A intake, blood pressure medication, parity
Sweden/ (Wirdefeldt et al. 2005)	Swedish Twin Registry, 1967 or 1973	2,380 /476, unrelated F and M	NR	inpatient discharge register or death certificates	Q	coffee intake (cups/d)	5+ vs. 0	1.03 (0.53–2.00)	0.78	birth year, sex, year answered the Q. Cases had two sets of controls: unrelated, twin	education, smoking, alcohol
		415 same-sex twins						1.27 (0.49–3.29)	0.80		

Abbreviations: PD, Parkinson's disease; OR, odds ratio; CI, confidence interval; F, female; M, male; Q, questionnaire; NR, not reported.

[a] Controls/PD cases

[b] Unadjusted

Table 12. Obesity and Parkinson's disease: Cohort studies.

Country/reference	Study name, baseline year	Population N/n[a], gender	Follow-up years	PD ascertainment	Measuring method of exposure	Exposure (unit)	Exposure categories compared	Adjusted result RR (95% CI)	*P* for trend	Adjustments
USA/ (Abbott et al. 2002)	Honolulu-Asia Aging Study (originally Honolulu Heart Study), 1965	7,990 /137, M	30	hospital records, death certificates or records of local neurologists	NR (unclear whether measured or self-reported)	baseline BMI (kg/m^2)	highest vs. lowest quartile	NR (just stated: NS)	<0.001	age, physical activity, smoking, coffee, caloric and fat intake, BMI, subscapular skinfold thickness
					skinfold thickness measurement with Lange calipers	tricep skinfold thickness (mm)	highest vs. lowest quartile	2.8 (1.4–5.6)		
						subscapular skinfold thickness (mm)	highest vs. lowest quartile	NR (just stated: NS)		
USA/ (Chen et al. 2004)	Nurses' Health Study, 1976; Health Professionals Follow-up Study, 1986	117,062 /202, F; 47,700/249, M	22 14	self-report, ascertained by treating physician or reviewing medical records	Q, self-reported weight and height (high validity reported)	baseline BMI (kg/m^2)	≥30 vs. <23	0.8 (0.6–1.2)[b]	0.3	age, caffeine, alcohol
						early adult BMI (kg/m^2)	≥27 vs. <20	1.0 (0.6–1.5)[b]	0.2	
						weight change (kg)	≥20.2 vs. <2.2	1.0 (0.5–2.2)[b]	0.6	
						waist-to-hip ratio	highest vs. lowest quintile	never smokers: 2.0 (1.1–3.6)[b]	<0.05	
Finland/ (Hu et al. 2006)	NR	23,439/254, F; 22 ,67/272, M	mean 18.8	registry on reimbursement for PD drugs, diagnosed by neurologist	measured height (without shoes) and weight (with light clothing)	baseline BMI (kg/m^2)	≥30 vs. <23	2.03 (1.44–2.85)	NR	age, sex, education, baseline year, physical activity, smoking, alcohol, coffee, tea, systolic blood pressure, cholesterol

Table 12. (continued)

Country/reference	Study name, baseline year	Population N/n[a], gender	Follow-up years	PD ascertainment	Measuring method of exposure	Exposure (unit)	Exposure categories compared	Adjusted result RR (95% CI)	*P* for trend	Adjustments
USA/ (Logroscino et al. 2007)	Harvard Alumni Health Study, 1988	10,812/106, M	10	self-report or death certificates	Q, self-reported weight and height	baseline BMI (kg/m^2)	≥25 vs. 22.5 to <25.0	0.86 (0.53–1.41)	NR	age, physical activity, smoking, coffee, tea, history of CVD or cancer in 1988
						BMI (kg/m^2) at college entry	≥25 vs. 22.5 to <25.0	0.49 (0.17–1.39)		
Singapore/ (Tan et al. 2008)	Singapore Chinese Health Study, 1993–1998	63,257/157, F and M	mean 7	self-report or hospital discharge database or PD registry, ascertained by reviewing medical records	NR	baseline BMI (kg/m^2)	NR	NR (just stated: NS	NR	NR
USA/ (Palacios et al. 2011)	Cancer Prevention Study II Nutrition Cohort, 1992	147,096/656, F and M	13	self-report, ascertained by treating physician or reviewing medical records	Q, self-reported weight and height	baseline BMI (kg/m^2)	≥30 vs. <23	1.00 (0.75–1.34)	0.79	age, education, physical activity, smoking, alcohol, caffeine, calories, dairy intake, pesticide exposure
						weight change (kg)	20.25 vs. 2.25 loss or gain	0.56 (0.39–0.82)	0.08	
						waist circumference (cm)	102.4 vs. 87.6	1.35 (0.95–1.93)	0.08	
Greece/ (Kyrozis et al. 2013)	EPIC-Greece, 1993–1999	25,407/88, F and M	mean 8.45	self-report, ascertained with self-reported telephone interview	interview	baseline BMI (kg/m^2)	10 kg/m^2 increment	0.86 (0.53–1.39)	0.53	age, sex, marital status, education, farming, physical activity, smoking, coffee, energy intake

Abbreviations: PD, Parkinson's disease; RR, relative risk; CI, confidence interval; F, female; M, male; Q, questionnaire; NR, not reported; NS, non-significant; BMI, body mass index; CVD, cardiovascular disease.

[a] Total population/PD cases

[b] Results are pooled RRs from the two cohorts

Table 13. Obesity and Parkinson's disease: Nested case-control studies.

Country/ reference	Study name, baseline year	Population N/n[a], gender	Follow-up years	PD ascertainment	Measuring method of exposure	Exposure (unit)	Exposure categories compared	Adjusted result OR (95% CI)	*P* for trend	Matching	Adjustments
USA/ (Paganini-Hill 2001)	Leisure World Cohort Study, 1981–1985	2,320/395, F and M	18	hospital discharge database, death certificates, or self-report	Q	BMI (kg/m^2)	NR	NR (just stated: NS)	NR	sex, birth date, vital status; if dead, death date	NR
China/ (Ma et al. 2006)	Nutritional Intervention Trial, 1986	340/85, F and M	14	screening: symptom questionnaire and neurological examination by neurologist	interview	BMI (kg/m^2)	≥23 vs. <20	0.43 (0.20–0.93)[b]	NR	sex, age, residential commune	
Sweden/ (Vikdahl et al. 2014)	Northern Sweden Health and Disease Study, 1986–2009	336/84, F and M	2–8	clinical examination by a neurologist, confirmed by another specialist	NR (measured at the time of the health-care visit)	waist:height ratio	NR	0.91 (0.77–1.07)	0.253	sex, age, year of health survey, subcohort, geographic area	age, physical activity, smoking, BMI

Abbreviations: PD, Parkinson's disease; OR, odds ratio; CI, confidence interval; F, female; M, male; Q, questionnaire; BMI, body mass index; NR, not reported; NS, non-significant.

[a] Controls/PD cases

[b] Unadjusted. Stated in the text: association persisted after controlling for smoking, gastric ulcer, and meat consumption

Table 14. Metabolic factors and Parkinson's disease: Cohort studies.

Country/reference	Study name, baseline year	Population N/n[a], gender	Follow-up years	PD ascertainment	Measuring method of exposure	Exposure (unit)	Exposure categories compared	Adjusted result RR (95% CI)	*P* for trend	Adjustments
Blood pressure										
USA/ (Grandinetti et al. 1994)	Honolulu-Asia Aging Study (originally Honolulu Heart Study), 1965	8,006/58, M	26	hospital records, death certificates or records of local neurologists	measured systolic and diastolic BP	hypertension	NR (interpreted as yes vs. no)	1.25 (0.68–2.28)	NR	age
USA/ (Simon et al. 2007)	Nurses' Health Study, 1976; Health Professionals Follow-up Study, 1986	121,046 /264, F; 50,833 /266, M	24 14	self-report, ascertained by treating physician or reviewing medical records	Q, self-reported history of physician diagnosed hypertension, or reported use of antihypertensive medication	history of hypertension	yes vs. no	0.96 (0.80–1.15)[b]	NR	age, smoking[c]
Finland/ (Qiu et al. 2011)	National FINRISK Study, 1972–2002	30,815 /371, F; 28,725 /423, M	mean 18.8	registry on reimbursement for PD drugs, diagnosed by neurologist	measured after 5-min rest, seated arterial BP, mercury sphygmomanometer, and reported use of antihypertensive medication	normal <130/80 mmHg, hypertension ≥140/90 mmHg or use of antihypertensives	hypertension vs. normal	F: 1.62 (1.09–2.42) M: 0.90 (0.63–1.28)	NR	age, baseline year, education, physical inactivity, smoking, alcohol, coffee, tea, BMI, diabetes mellitus, total cholesterol
Singapore/ (Tan et al. 2008)	Singapore Chinese Health Study, 1993–1998	63,257 /157, F and M	mean 7	self-report or hospital discharge database or PD registry, ascertained by reviewing medical records	Q, self-reported medical history	hypertension	NR (interpreted as yes vs. no)	NR (just stated: NS)	NR	NR

Table 14. (continued)

Country/reference	Study name, baseline year	Population N/n[a], gender	Follow-up years	PD ascertainment	Measuring method of exposure	Exposure (unit)	Exposure categories compared	Adjusted result RR (95% CI)	*P* for trend	Adjustments
HDL cholesterol										
Netherlands/ (de Lau et al. 2006b)	Rotterdam Study, 1990–1993	6,465 /87, F and M	mean 9.4	PD diagnosed by neurologist at the follow-up examination	non-fasting blood samples, serum HDL determined by automated enzymatic procedure	serum HDL (mmol/l)	highest vs. lowest quartile	overall: 1.81 (0.96–3.42) M: 1.38 (0.56–3.43) F: 2.69 (1.11–6.49)	NR	age, sex[d]
USA/ (Huang et al. 2008)	Honolulu-Asia Aging Study (originally Honolulu Heart Study), 1965 (blood specimens 1991–1993)	3,233/41, M	20	hospital records, death certificates or records of local neurologists; after 1991, neurologic examination	NR (fasting blood specimens obtained, lipid determination method not reported)	HDL cholesterol level	NR	NR (just stated: NS)	NR	NR
Triglycerides										
-										
Glucose										
-										

Abbreviations: PD, Parkinson's disease; RR, relative risk; CI, confidence interval; F, female; M, male; Q, questionnaire; BP, blood pressure; NR, not reported; NS, non-significant; BMI, body mass index; HDL, high-density lipoprotein.

[a] Total population/PD cases

[b] Results are pooled RRs from the two cohorts

[c] Results were similar when further adjusted for caffeine and alcohol intake, BMI, history of high cholesterol or diabetes

[d] Results were similar when further adjusted for smoking, coffee, dietary vitamin E, BMI, apolipoprotein E genotype, baseline lipid-lowering drug use

Table 15. Metabolic factors and Parkinson's disease: Nested case-control studies.

Country/ reference	Study name, baseline year	Population N/n[a], gender	Follow-up years	PD ascertainment	Measuring method of exposure	Exposure (unit)	Exposure categories compared	Adjusted result OR (95% CI)	*P* for trend	Matching	Adjustments
Blood pressure											
USA/ (Paganini-Hill 2001)	Leisure World Cohort Study, 1981–1985	2,320/395, F and M	18	hospital discharge database, death certificates, or self-report	Q, self-reported	hypertension	yes vs. no	0.71 (0.56–0.89)[b]	NR	sex, birth date, vital status; if dead, death date	smoking, alcohol, coffee, vitamin C and A intake, parity
						current BP medication use	yes vs. no	0.62 (0.48–0.80)			
China/ (Ma et al. 2006)	Nutritional Intervention Trial, 1986	340/85, F and M	14	screening: symptom questionnaire and neurological examination by neurologist	interview, self-reported	hypertension	NR (presumably yes vs. no)	NR (just stated: NS)	NR	sex, age, residential commune	NR
Sweden/ (Vikdahl et al. 2014)	Northern Sweden Health and Disease Study, 1986–2009	336/84, F and M	2–8	clinical examination by a neurologist, confirmed by another specialist	NR (measured at time of health-care visit)	systolic BP (mmHg)	NR	0.98 (0.96–0.99)	0.04	sex, age, year of health survey, subcohort, geographic area	age, physical activity, smoking, BMI
HDL cholesterol											
-											
Triglycerides											
Sweden/ (Vikdahl et al. 2014)	same as above	same as above	same as above	same as above	NR (assessed at time of health-care visit)	serum triglycerides (mmol/l)	NR	0.64 (0.41–1.01)	0.053	same as above	same as above
Glucose											
Sweden/ (Vikdahl et al. 2014)	same as above	same as above	same as above	same as above	same as above	fasting blood glucose	NR	NR (just stated no difference)	NR	same as above	same as above

Abbreviations: PD, Parkinson's disease; OR, odds ratio; CI, confidence interval; F, female; M, male; Q, questionnaire; BP, blood pressure; NR, not reported; NS, non-significant; BMI, body mass index.

[a] Controls/PD cases

2.2.6 Summary of literature review

It seems that the epidemiologic evidence for most of the factors examined is inconclusive, as was also concluded by both de Lau and Breteler (2006a) and Wirdefeldt et al. (2011). Thus far, older age and smoking habits are the only risk or protective factors for PD that have consistently been found across studies (see de Lau and Breteler 2006a). For coffee consumption, the results have been rather consistent for reporting an inverse association, but further evidence is needed; for example, acquisition of supportive evidence from clinical and animal studies is ongoing.

For physical activity and alcohol consumption, the number of studies is growing, but the results have been inconclusive, finding no association or a weak inverse association. Furthermore, there are a few factors with some consistency in findings across studies (e.g. milk consumption, vitamin E and polyunsaturated fat intake, and serum uric acid concentration), but the number of studies are too limited. For other factors, the results have been contradictory and the number of studies is low.

Methodological differences (especially in PD ascertainment) and incomparable reporting complicates summarizing the results. An agreed minimum set of adjustments, for example age, sex, and smoking, would be helpful for comparisons across studies. Furthermore, potential effect-modifying factors should be studied systematically. More prospective studies are needed to further examine the epidemiology of PD. Future studies should also acknowledge the preclinical phase of PD in analyses.

3 Aims of the study

The general objective of this study was to determine whether diet, other lifestyle factors, and metabolic health predicted the incidence of Parkinson's disease in population-based cohorts with a prospective study design.

The specific study aims were to examine:

- The association between food consumption, overall quality of diet, and the risk of PD (Study I);

- The association between lifestyle factors (leisure-time physical activity, smoking, alcohol consumption, and coffee consumption) and the risk of PD (Studies II and III);

- The association between metabolic health, especially body mass index, and the risk of PD (Studies II and IV).

4 Population and methods

4.1 Study populations

The Social Insurance Institution conducted the Finnish Mobile Clinic Health Examination Survey (FMC) between 1966–1972. The health examinations were carried out by mobile field clinics. The Social Insurance Institution continued to study the health of the Finnish population with the Finnish Mobile Clinic Follow-up Survey (FMCF), conducted in 1973–1976, and the Mini-Finland Health Survey, 1978–1980. These studies are well described on the webpages of the Finnish Mobile Clinic Surveys (https://www.thl.fi/fi/tutkimus-ja-asiantuntijatyo/vaestotutkimukset/autoklinikka-tutkimukset).

Study I is based on the FMC. A total of 62,440 men and women aged 15 or over were invited to take part in the study, and 82.5% participated (Aromaa 1981). The baseline examinations were carried out in 31 rural, industrial, or semi-urban populations (Figure 2). The sample was not representative of the Finnish population, but followed the age distribution of the general population. As part of the main study, a dietary history interview was performed for 10,054 selected subjects (Järvinen 1996; Seppänen et al. 1973). Of these, participants aged 40–79 years were included in the Study I (n=4,738).

Studies II and III are based on the FMCF (Reunanen et al. 1983), which was conducted in subpopulations of the baseline FMC study populations in 12 municipalities around Finland (Figure 3). Every third subject of those invited to the FMC, aged 20 years or older, was also invited to participate in the FMCF. Thus, 24,833 subjects were invited, and a total of 19,518 subjects were re-examined (78.6% response rate). Studies II and III included only those participants between ages 50–79 (n=7,246).

Study IV is based on the Mini-Finland Health Survey carried out in 40 areas of Finland (Figure 4) (Aromaa et al. 1989; Lehtonen and Kuusela 1986). The sample was a stratified two-stage cluster sample representative of the Finnish population of adults aged 30 years and over (n=8,000). A total of 7,217 subjects (90%) participated in the health examination. Of these, participants between ages 30–79 were included in the present study (n=7,041).

In all studies, subjects identified as PD cases at baseline were excluded. Additionally, subjects who reported the use of antipsychotic medication due to psychotic disorders (see chapter 4.3.2 for details) were excluded. Thus, the final study populations included:

- 4,524 subjects in Study I

- 6,715 subjects in Study II

- 6,710 subjects in Study III, as subjects with missing information on coffee consumption were further excluded

- 4,828 subjects in Study IV

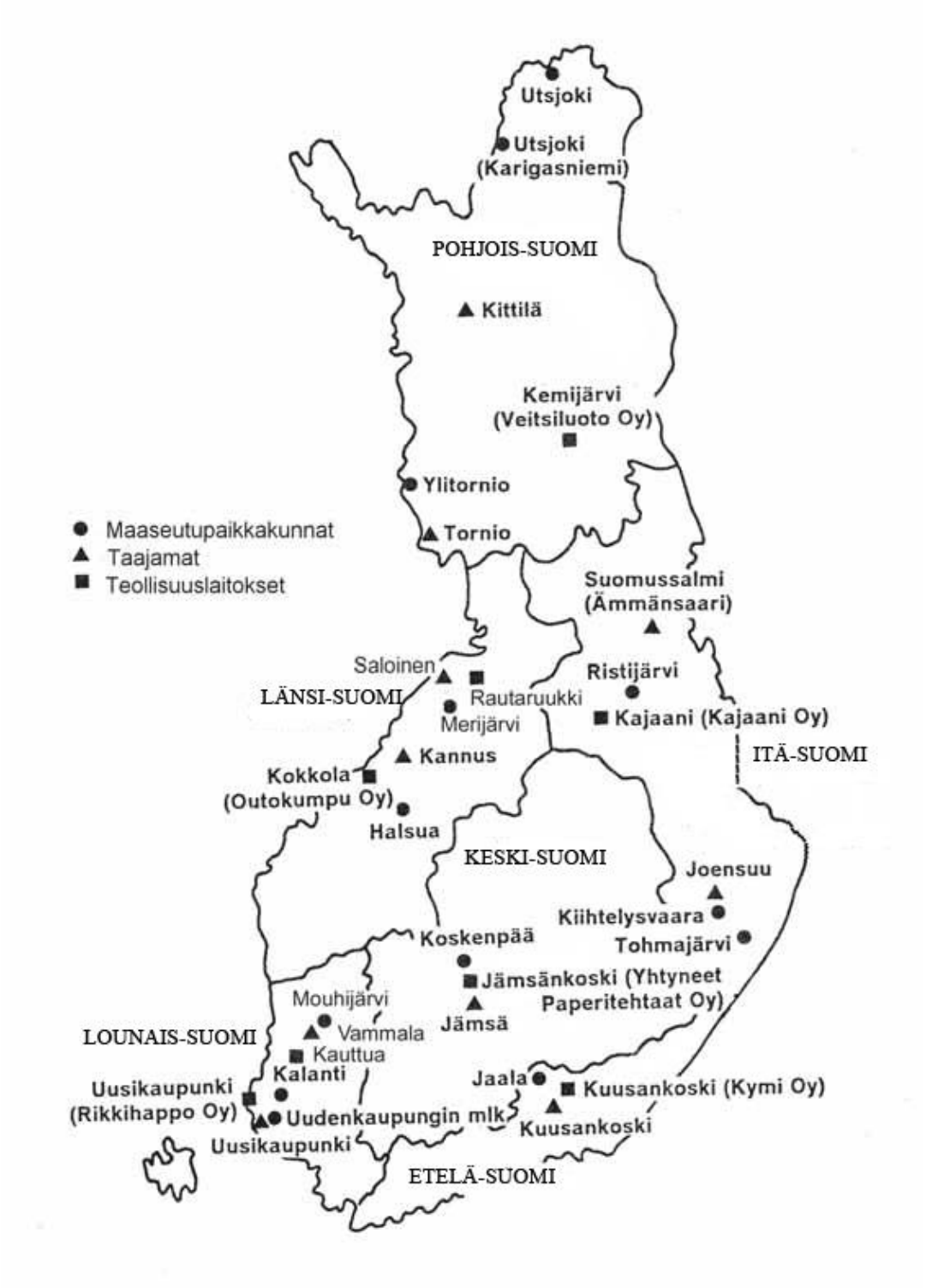

Figure 2. The areas of baseline examinations in the Finnish Mobile Clinic Health Examination Survey in 1966–1972.

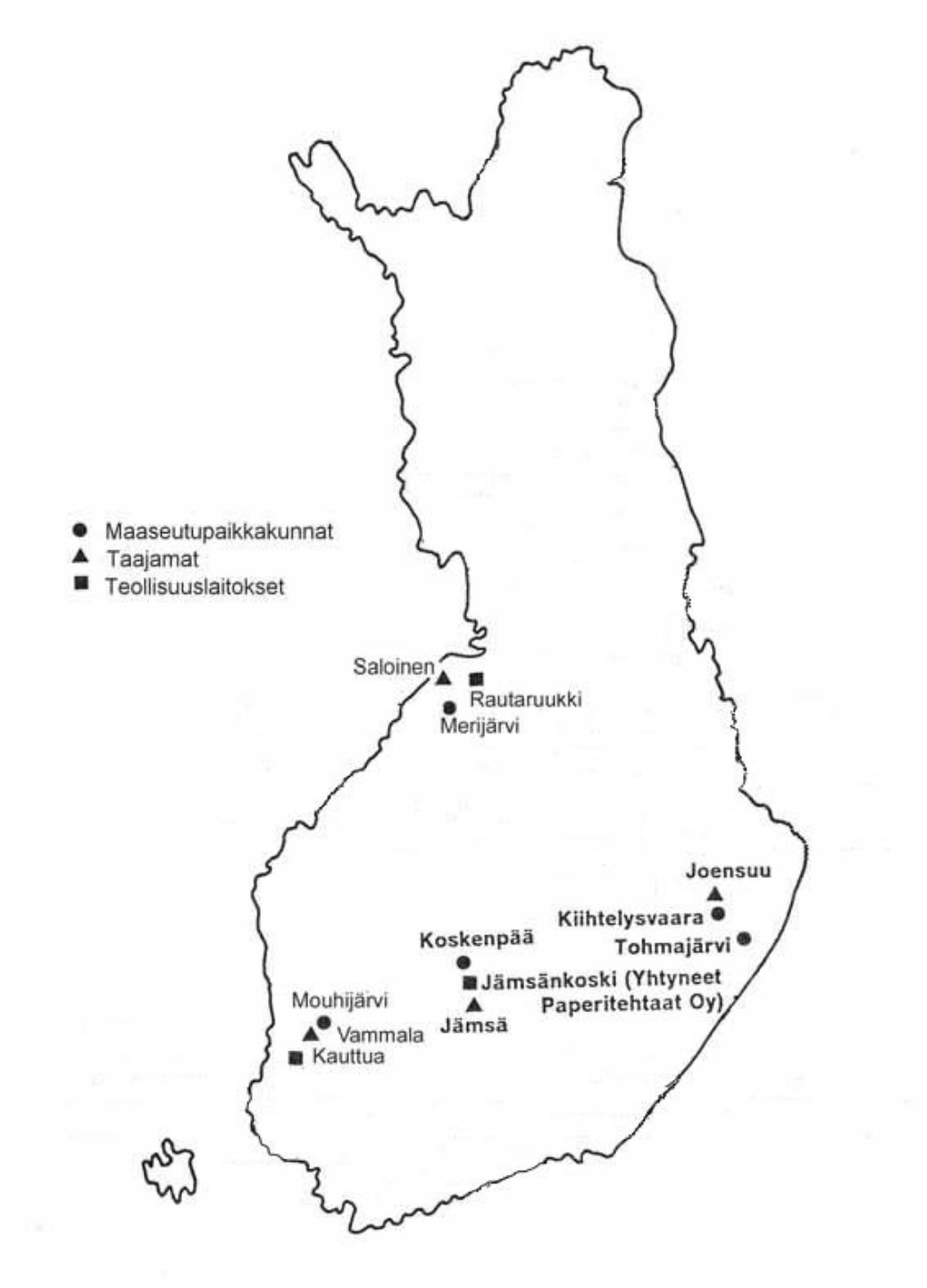

Figure 3. The areas of baseline examinations in the Finnish Mobile Clinic Follow-up Survey in 1973–1976.

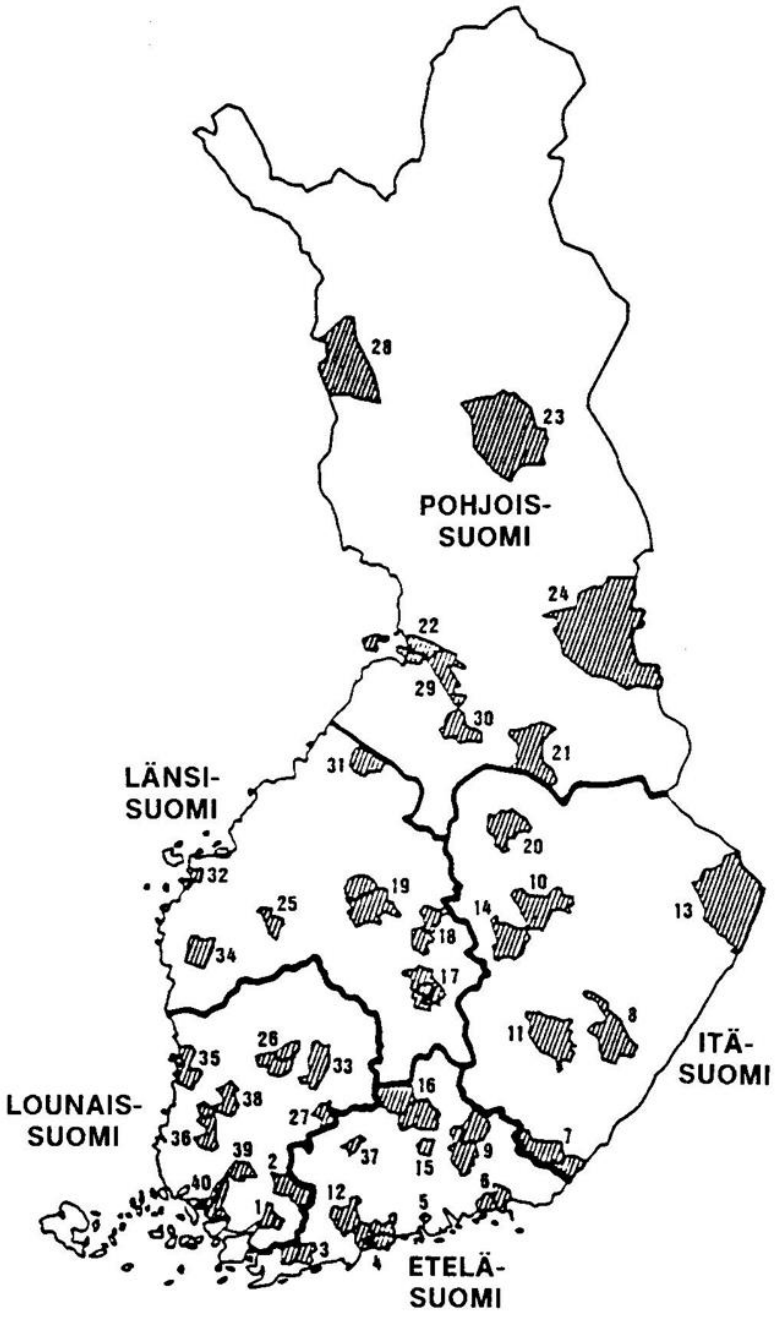

Figure 4. The areas of baseline examinations in the Mini-Finland Health Survey in 1978–1980.

4.1.1 Ethical questions

The three surveys used in this study precede the current legislation on ethics in medical research. In all three studies, the participants were fully informed about the study. They participated voluntarily and the use of the information for medical research was explained to them. Agreeing to participate in the baseline health examination was taken to indicate informed consent. The follow-up study using record linkage was approved by the Institutional Review Board of the National Institute for Health and Welfare on June 8, 2011. The Social Insurance Institution of Finland approved the linkage to their registers (Kela 9/500/2011). All researchers in this study were obligated to professional confidentiality and no identifiable information is given to third parties.

4.2 Measurement methods

4.2.1 Measures of primary exposure variables

Food consumption and diet quality (Study I), the FMC Survey

At the baseline examinations of the FMC, the total habitual food consumption of the participants during the previous year was assessed using a dietary history interview (Koskinen 1975; Seppänen et al. 1973; Järvinen 1996). Trained interviewers used a questionnaire which included over 100 food items and mixed dishes common in the diet of Finns at the time. The frequency of food items was reported per day, week, month, or year, according to the choice of the respondent. Food models were used to help in recalling portion sizes. Furthermore, the methods of food preparation were inquired about (for example, the interview form included separate rows for smoked fish and fried fish). Several of the questions were open-ended and intended to be specified by the respondent.

Individual consumption of food items and mixed dishes was converted into grams/day. Then the ingredients of mixed food dishes were broken down into their component foods using a recipe file. This file, including the recipes of mixed dishes, was based on contemporary Finnish cookbooks and data collected in food consumption studies. Next, the intakes of separate food items appearing in the original interviews and those derived from mixed food dishes were combined and calculated per day. Finally, the intakes of nutrients from all food items were computed using a food composition file. Originally, the food composition database was compiled utilizing the contemporary Finnish food composition tables (Turpeinen and Roine 1967). During the late eighties, the food composition data were updated and new values were calculated based on the nutrient composition book published by the Finnish Social Insurance Institution (Rastas et al. 1989). The methods for the dietary study have also been described in detail on the webpage for the Finnish Mobile Clinic Surveys (https://www.thl.fi/fi/tutkimus-ja-asiantuntijatyo/vaestotutkimukset/autoklinikka-tutkimukset/autoklinikan-moniseulontatutkimus/aineisto/kenttamittausaineisto/kyselyt-ja-haastattelut).

In Study I, the whole diet was represented with consumption of 24 food groups and items (g/d): total grains, rye, wheat, whole grains, total vegetables, legumes and nuts, potato, roots, total fruits and berries, fresh fruits, berries, margarines, oils and mayonnaise, butter, total milk and milk products, milk, cheese, fermented milk products, total meat and meat products, red meat, processed meat and sausages, poultry, ratio of white meat to red meat, fish, eggs, sugar and sugar rich condiments. The Appendix Table 2 presents the details of the food groups and items. Intake was divided into tertiles for analyses due to the

absence of a predefined hypothesis for cut-off points, and to avoid the assumption of a linear association between exposure and PD.

For Study I, a dietary index was created based on the definition of the Alternate Healthy Eating Index (AHEI), an index developed to measure adherence to the Dietary Guidelines for Americans (McCullough et al. 2002). A few modifications were made to adjust the AHEI index to the Finnish population in our study. We aimed for a similar definition whenever possible, but in comparison with AHEI, information on multivitamin use and alcohol consumption could not be included since these variables did not exist in the FMC data. Thus, the current dietary index, modified AHEI (mAHEI), included the following seven components: vegetables (not potato), fresh fruits (not berries), nuts and legumes, the ratio of white (fish and poultry) to red meat, whole grains (products containing > 25% whole grain), the ratio of polyunsaturated to saturated fat, and trans fats (Study I). The intakes of components were then divided into quintiles to assign scores. The first six components received scores in an ascending order, so that one point was assigned for intakes in the lowest quintile and five points for intakes in the highest quintile. The trans fats component received scores in descending order, with the lowest quintile gaining a value of five points and the highest quintile a value of one point. The total score, thus, ranged from 7 (worst) to 35 (best). A higher score suggested a higher adherence to a healthy diet. The reasoning for constructing the mAHEI is further discussed in chapter 6.4.2.

Lifestyle factors (Studies II and III), the FMCF Survey

As part of the FMCF, all subjects completed a mailed, self-administered, health questionnaire (Reunanen et al. 1983). The questionnaire is available on the webpage for the Finnish Mobile Clinic Surveys (https://www.thl.fi/documents/10531/1925652/AU01_Peruskyselylomake.PDF/4b31c7c2-a1c6-44e6-a666-ea46c6aa9087). The questionnaire, which was checked by a trained study nurse at the baseline examinations, provided information on leisure-time physical activity, smoking, and alcohol and coffee consumption.

Participants were asked to classify their leisure-time physical activity during a typical week into one of four categories: 1) none; 2) light physical activity for at least four hours per week (e.g. walking, cycling); 3) heavy physical activity for at least three hours per week (e.g. jogging, skiing, vigorous gardening); or 4) regular heavy physical activity several times a week. The last two alternatives were combined, classifying physical activity into three categories (none, light, heavy).

Furthermore, based on detailed questions about smoking habits, the participants were classified as: never smoker, past smoker, or current smokers (the latter category combining the following: uses cigar or pipe but not cigarettes, smokes less than 15 cigarettes per day, smokes 15 to 24 cigarettes per day, or smokes at least 25 cigarettes per day). Past smokers were classified as those who reported ever smoking for at least a one year time period, but who currently do not smoke.

Alcohol consumption was assessed through ten questions regarding the amount, frequency, and type of alcohol consumed. A participant's total alcohol intake was calculated as the sum of the contribution from beer, wine, and liquor and was expressed in grams of ethanol per day. The alcohol content by weight was considered to be 3.6% for beer, 8.9% for wine, and 35.0% for liquor. The cut-off points for categorization of alcohol consumption could not be set against recommended values of risk-level intake because alcohol consumption in this population was very low (median, 0 g/d). Thus, non-users were categorized as one group, and a consumption of approximately 3 alcohol portions per week was chosen to divide alcohol users in moderate (<5 g/d) and heavy consumption (≥5 g/d).

The health questionnaire enquired about coffee consumption with an open-ended question as the average number of cups per day.

The information on BMI was obtained from the baseline health examinations of the FMCF by measuring height (without shoes) and weight (in light indoor clothing). The measurement of weight was rounded to the nearest full kilogram, and the weight of clothing was taken into account by subtracting 2 kg from the measurements during winter time examinations and 1 kg during summer time. BMI was calculated as weight in kilograms divided by the square of the height in meters (kg/m^2).

Metabolic health (Study IV), The Mini-Finland Health Survey

The Mini-Finland Health Survey included a baseline health examination (Aromaa et al. 1989) where casual blood pressure was measured twice with a 1.5 minute interval by the auscultatory method. For the current study, the mean of the two blood pressure measurements was used in analyses. Furthermore, overnight fasting blood samples were taken and stored at -20 °C (96.7% of the participants had at least an 11 hour fast, mean duration of fast was 16.8 h, SD 3.5). Serum triglyceride, serum HDL cholesterol, and fasting plasma glucose concentrations were determined a few weeks after the samples were taken. Serum triglyceride concentration was determined using the fully enzymatic method (Boehringer, Mannheim, Germany) (Wahlefeld 1974). In the HDL cholesterol analysis, LDL and VLDL was first precipitated with Mg-dextrane sulphate (Kostner 1976), then HDL cholesterol was determined from the supernatant by a modification of the direct Liebermann-Burchard method without a so-called serum-blank subtraction (Carr and Drekter 1956). Fasting plasma glucose was determined using a glucose oxidase method (Boehringer, Mannheim, Germany) (Werner et al. 1970).

At the baseline examinations, weight (in light indoor clothing, without shoes) was measured by a frequently calibrated lever balance. Height was measured without shoes and with the back against a wall. BMI was calculated as weight in kilograms divided by the square of the height in meters (kg/m^2).

The definition of metabolic syndrome and the cut-off values for categories of the components of it were based on the harmonized definition of metabolic syndrome (Alberti et al. 2009). BMI was used as a proxy measure in the definition of metabolic syndrome by replacing the waist circumference category 'normal' with a BMI of <25 kg/m^2 and the category 'large' with a BMI of ≥25 kg/m^2, since the present data did not include information on waist circumference. For this reason, we used the Health 2000 data (Aromaa et al. 2002), a representative sample of Finnish adults, to examine the validity of BMI for the cut-off point 25 kg/m^2 by using waist circumference with a cut-off value of ≥94 for men and ≥80 for women as the reference. We found that BMI had a reasonable sensitivity (82.5%) and specificity (85.3%), and, accordingly, used BMI as a proxy measure. Furthermore, the use of this proxy measure was supported by a recent cohort study, where the relative risk of diabetes for individuals with metabolic syndrome defined according to both the original definition and the proxy definition did not notably differ (RR 6.70, 95% CI 3.61–12.4 for original definition, and RR 6.78, 95% CI 3.72–12.4 for proxy definition) (Laaksonen et al. 2010).

The criterion for the metabolic syndrome was the presence of any three or more of the following five components: BMI ≥25 kg/m^2, elevated mean blood pressure (SBP ≥130 mmHg or DBP ≥85 mmHg or antihypertensive drug treatment), high serum triglycerides (≥1.7 mmol/L), low serum HDL cholesterol (<1.3 mmol/L in women and <1.0 mmol/L in men), and high fasting plasma glucose (≥5.6 mmol/L). The general criterion and cut-off values follow those presented by Alberti et al. (2009), but the modified criterion used here (with the BMI proxy measure) followed the work of Laaksonen et al. (2010).

4.2.2 Measures of covariates

The comprehensive health examinations made at the baselines of the FMC, FMCF, and Mini-Finland Health Survey provided an ample amount of information on potential confounding factors. Despite all the available data from these surveys, only those factors used in current studies (I–IV) are mentioned here. However, it should be noted that the questionnaires used in the FMC and FMCF were not exactly similar. Thus, both classifications of the variables and the covariates used in the models differ between the studies.

The factors used as covariates in individual studies, and their categorizations, are listed in the original articles in detail (Studies I–IV). Below, the assessment of these factors is described in general.

Sociodemographic and lifestyle factors

In both the FMC (Aromaa 1981) and the FMCF (Reunanen et al. 1983), trained study nurses reviewed, in-person, the mailed, self-administered health questionnaire participants were asked to complete prior to the baseline examination. Sociodemographic factors obtained from the health questionnaire included e.g. age, sex, education, marital status, geographical area, community density, and occupation. Additionally, previous and current illnesses (e.g. diabetes and cardiovascular diseases), use of medication (e.g. use of antipsychotics) and other health-related information (e.g. parity) were inquired about. In the FMC, lifestyle factors collected in the health questionnaire included smoking and leisure-time physical activity. The FMC did not include questions on alcohol or coffee consumption. The FMCF, however, provided information on leisure-time physical activity, smoking, and alcohol and coffee consumption, as described above.

In the Mini-Finland Health Survey, the background information was gathered both from a health interview and a self-administered questionnaire. They provided information on, for example, age, sex, education, smoking, alcohol consumption, leisure-time physical activity, coffee consumption, previous diseases (e.g. diabetes and cardiovascular diseases), and antihypertensive medication at baseline.

Biological factors

In the FMC, baseline examinations included measurements of casual blood pressure using the auscultatory method (Aromaa 1981), and collection of venous blood samples. Serum total cholesterol concentrations were determined via an autoanalyzer modification (Auto-Analyzer Methodology N-24a and N-77; Technicon, Tarrytown, NY, USA) of the Liebermann–Burchard reaction (Huang et al. 1961). Additionally, height (without shoes) and weight (in light indoor clothing) were measured and BMI (kg/m^2) was calculated.

In the FMCF, blood pressure was measured in the seated position after a 5-min rest, using a semiautomatic device (Elag BPM-A) (Aromaa 1981). Serum samples were taken and the cholesterol concentrations determined by an autoanalyzer modification of the Liebermann-Burchard reaction (Huang et al. 1961).

Baseline examinations of the Mini-Finland Health Survey included blood pressure measurements and blood sample collection and analyses as described above (chapter 4.2.1). Also, in 2002, serum 25-hydroxyvitamin D concentration was determined using radioimmunoassay (DiaSorin, Stillwater, Minnesota, USA), with an inter-assay coefficient of variation (CV) of 7.8%. In the absence of a predefined hypothesis, a median value was used to dichotomize the variable on serum vitamin D concentration.

4.2.3 Reliability of the measures

Table 16 describes the repeatability of the exposure measures used in the present study. Previous studies from the FMC, FMCF, and Mini-Finland Health Survey have examined both long-term and short-term repeatability. Variables that were not examined previously were studied as part of the current thesis work.

The intraclass correlation coefficients (ICC) for the short-term repeatability were above 0.6 for the mAHEI index as well as for most of the dietary factors included in this study (Table 16). This can be considered as acceptable agreement between the repeated measurements, and as concluded by Järvinen et al. (1993), the dietary patterns of examinees were sufficiently stable to be compatible with the needs of epidemiological follow-up studies.

Measurement on berries and eggs, however, showed lower ICCs (r= 0.36 and 0.47, respectively), which may still be considered as fair agreement. The consumption of berries and eggs was rather low, so these results may reflect the finding that foods eaten less often are not recalled as reliably as those eaten regularly (Nomura et al. 1976).

In previous studies on food intake measured by repeated food frequency questionnaires at the interval of 3–12 months, average correlation coefficients have ranged from 0.5 to 0.7 (Willett and Lenart 1998).

As could be expected, the long-term agreement between the repeated measurements declined for the mAHEI index and all the dietary factors (Table 16). This is probably due to the effect of real changes in diet over time, in addition to the errors in recalling the participant's habitual diet. In the long-term, most of the ICCs here varied between 0.2 and 0.5. The berry consumption and polyunsaturated:saturated ratio, however, had poorer agreement (r= 0.10 and 0.12, respectively). Previous studies on food intake measured repeatedly with more than a one-year interval have showed average correlation coefficients between 0.3 and 0.5 (Willett and Lenart 1998).

For physical activity, information on short-term repeatability was available. The agreement between the two measurements had only fair agreement (r=0.38), which may be a concern. As with diet, measuring physical activity with questionnaires is challenging. Instead, smoking, alcohol consumption, and coffee consumption had relatively good stability with ICCs ranging mostly between 0.7 and 0.8 (Table 16).

The short-term repeatability was not available for height and weight in the Mini-Finland Health Survey and was thus reviewed from the FMC. Measurements on both height and weight had excellent short-term repeatability, with ICCs above 0.9 (Table 16). Accordingly, BMI had excellent repeatability too (r=0.96) when measured with one-year intervals in the Mini-Finland Health Survey.

The components of metabolic syndrome were measured reliably too, as the short-term ICCs varied between 0.7 and 0.8 (Table 16). The ICCs declined slightly when measurements were repeated at one-year intervals, but were all still above 0.7.

Table 16. Repeatability of the primary exposure variables used in the present study.

Variable	Short-term repeatability			Long-term repeatability		
	N	Measure[a]	Reference	N	Measure[a]	Reference
	FMCF (interval between measurements 4–8 months)			**FMC vs. FMCF** (interval between measurements 4–7 years)		
Diet						
Cereals	93	0.62	[b]	1,844	0.39	[b]
Vegetables	93	0.63	[b]	1,844	0.47	[b]
Fruits	93	0.64	[b]	1,844	0.41	[b]
Berries	93	0.36	[b]	1,844	0.10	[b]
Milk products	93	0.68	[b]	1,844	0.54	[b]
Meat products	93	0.72	[b]	1,844	0.47	[b]
Fish	93	0.72	[b]	1,844	0.39	[b]
Eggs	93	0.47	[b]	1,844	0.28	[b]
Sugar and sweets	93	0.69	[b]	1,844	0.33	[b]
P:S ratio	93	0.75	[b]	1,844	0.12	[b]
mAHEI index	93	0.61	[c]	1,844	0.49	[c]
Lifestyle factors						
Physical activity	282	0.38	[c]	NA		
Smoking	NA			17,631	0.82	[c]
Alcohol consumption	286	0.75	[c]	NA		
Coffee consumption	286	0.77	[d]	NA		
Biological measures						
	FMC (interval between measurements few months)					
Height	366	0.995	[e]			
Weight	366	0.98	[e]			
	Mini-Finland Health Survey (interval between measurements 3 months)			**Mini-Finland Health Survey** (interval between measurements 1 year)		
Body mass index	NA	NA		417	0.96	[f]
Systolic blood pressure	1,314	0.77	[f]	373	0.75	[f]
Diastolic blood pressure	1,314	0.72	[f]	373	0.75	[f]
Serum HDL cholesterol	1,315	0.78	[f]	42	0.76	[f]
Fasting plasma glucose	1,313	0.74	[f]	373	0.70	[f]
Serum triglycerides	1,316	0.83	[f]	373	0.73	[f]

Abbreviations: FMC, Finnish Mobile Clinic Health Examination Survey; FMCF, Finnish Mobile Clinic Follow-up Survey; y, year; P/S, polyunsaturated/saturated; mAHEI, modified Alternate Healthy Eating Index; F, female; M, male; NA, not available; HDL, high-density lipoprotein.

[a] Intraclass correlation coefficient: r for continuous and Kappa for categorized variables (i.e. physical activity and smoking)

[b] (Järvinen et al. 1993)

[c] Katri Sääksjärvi, unpublished (analyzed for this thesis)

[d] (Sääksjärvi et al. 2010)

[e] (Heliövaara and Aromaa 1980)

[f] Paul Knekt, unpublished (personal communication 2015)

In addition, the suitability of the health questionnaire in measuring coffee consumption was assessed in a subpopulation of participants from the FMCF by determining the agreement between the health questionnaire and a 1-year dietary history interview (n=4,341). The ICC was 0.86 for the agreement between the health questionnaire and the dietary history interview (Sääksjärvi et al. 2010).

The relative validity of the dietary history interview used here has not been evaluated against other dietary methods. Previously, average correlation coefficients ranging from 0.3 to 0.8 are typically seen in validation studies of food frequency methods (Willett and Lenart 1998).

4.3 Case ascertainment

4.3.1 Identification and prevalence of PD cases

PD cases were ascertained through the nationwide Drug Reimbursement Register of the Social Insurance Institution (SII) which stores data on patients receiving medication reimbursement using a unique personal identity number given to all Finnish residents. In this study, PD was defined as the World Health Organization's International Classification of Diseases (ICD-10) code G20, which means only primary, idiopathic Parkinson's disease, and thus secondary or other forms of parkinsonism were not included.

The information on PD cases was retrieved from the SII's register using the reimbursement right code 110. To obtain this allowance for free drug treatment, PD patients must apply for it and attach a certificate from a treating neurologist describing the clinical diagnostic criteria, including symptom history and findings from clinical examinations (stating the presence of characteristic motor manifestations such as resting tremor, bradykinesia and/or muscle rigidity, along with other findings). The allowance is granted after inspection of the claim by another neurologist at the SII. The medication allowance is not granted for patients with, for example, essential tremor, intention tremor, or parkinsonism caused by neuroleptics.

The prevalence of PD in the Finnish population

The prevalence of PD cases, based on the information retrieved from the Drug Reimbursement Register of the SII, is presented in Figures 5–8, covering those years included for follow-up in the present study. A direct age-adjustment was applied for calculation of the prevalence rates using the age distribution of the population in the year 1990. The prevalence of PD was calculated by including all patients receiving medication reimbursement for PD and then excluding those who also received medication reimbursement for psychotic disorders (reimbursement right code 112).

The decision to exclude those PD cases who also received medication reimbursement for psychotic disorders was made in order to remove cases potentially suffering from drug-induced secondary parkinsonism. Drugs that block the action of dopamine (dopamine antagonists), such as neuroleptic drugs used to treat schizophrenia and other psychotic disorders, are likely to cause parkinsonism (see Lopez-Sendon et al. 2013). Parkinsonism can occur from the use of any of the various classes of neuroleptics, but the highest risk is for first-generation antipsychotics (i.e. typical antipsychotics: haloperidol, prochlorperazine, thioxantenes, amisulpride, flupentixol, fluphenazine, levomepromazine, pimozide, promazine, sulpiride, thioridazine, zuclopenthixol)(see Lopez-Sendon et al. 2013).

The prevalence of PD was considerably lower after excluding the antipsychotic medication users (Figure 5). The difference in the prevalence between antipsychotic medication users and non-users was greatest during the time period between the end of the 1970's and 1995. It could be speculated that the reduced difference after 1995 is because the use of classical neuroleptics has been replaced by second- or third-

generation antipsychotics (see Rimon and Leinonen 2002), which have a lower risk of inducing secondary parkinsonism (see Lopez-Sendon et al. 2013).

In this study, any further reference to the PD cases during the follow-up refers to a patient group from which cases with the medication reimbursement right for psychotic disorders have been excluded.

The prevalence of PD increased during the 1970's (Figure 6), though presumably this is not solely due to actual rise in prevalence of the disease, but also due to changes in the practices of clinical diagnosis of PD, leading to improved diagnostic accuracy of the disease. However, improvements in the medical treatment of PD, especially the introduction of L-dopa, have also had an effect on the prevalence rates, by altering the clinical course and increasing the life-expectancy of these patients (see further discussion in chapter 6.4.3). Furthermore, the prevalence was higher in men than in women (Figures 7 and 8).

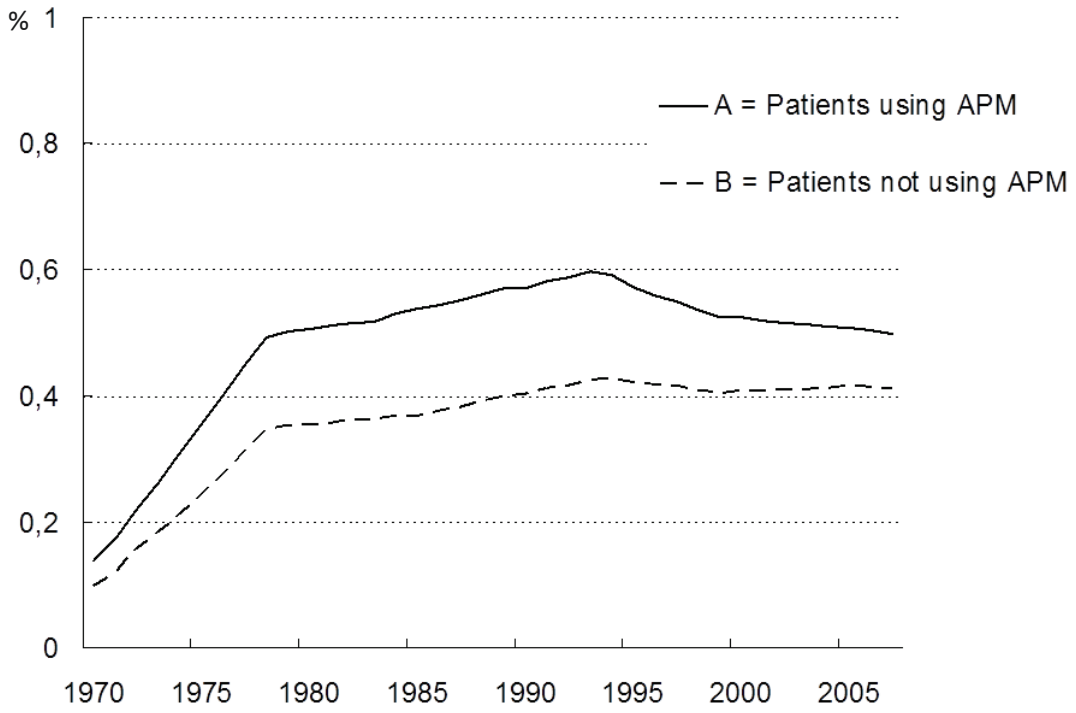

Figure 5. Age-adjusted prevalence of Parkinson's disease in the Finnish population (1970–2007) by use of antipsychotic medication, based on the Drug Reimbursement Register of the Social Insurance Institution [A=patients using antipsychotic medication (APM), B=patients not using antipsychotic medication (APM)].

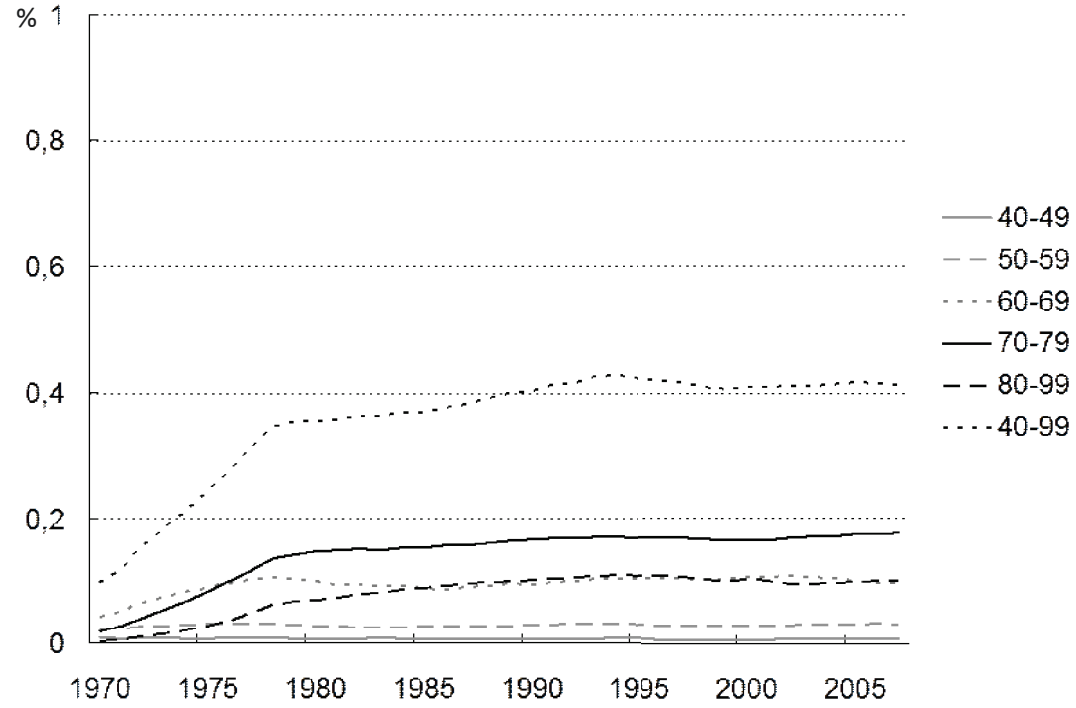

Figure 6. Age-adjusted prevalence of Parkinson's disease (excluding patients using antipsychotic medication) in the Finnish population (1970–2007) by age group, based on the Drug Reimbursement Register of the Social Insurance Institution.

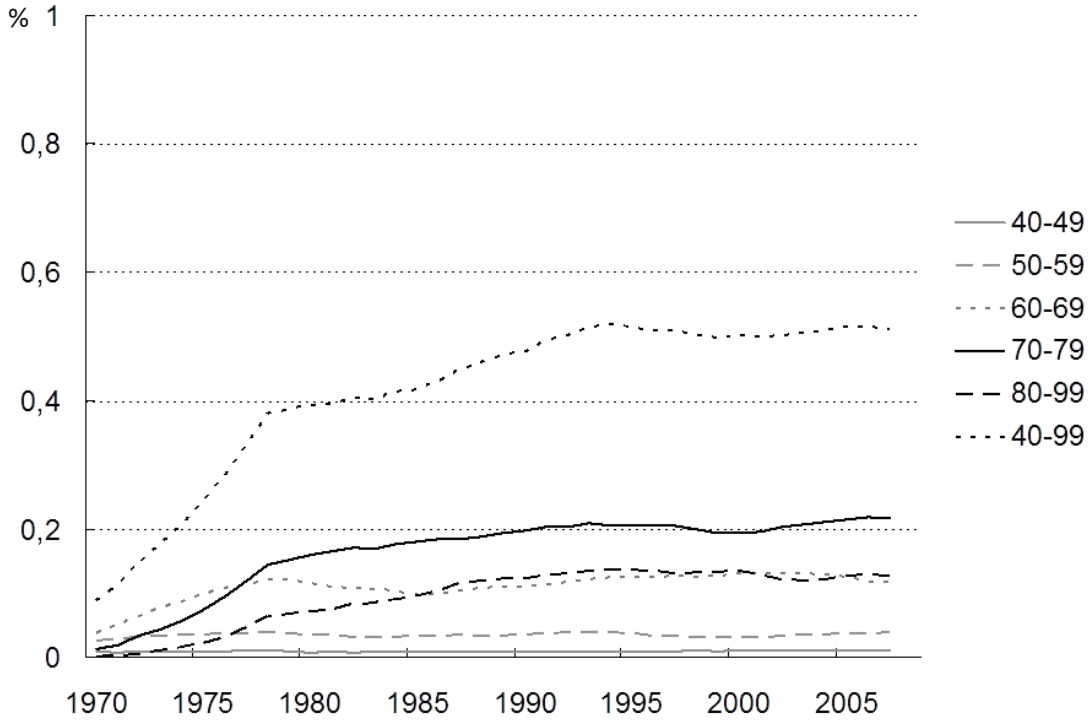

Figure 7. Age-adjusted prevalence of Parkinson's disease in **men** (excluding patients using antipsychotic medication) in the Finnish population (1970–2007) by age group, based on the Drug Reimbursement Register of the Social Insurance Institution.

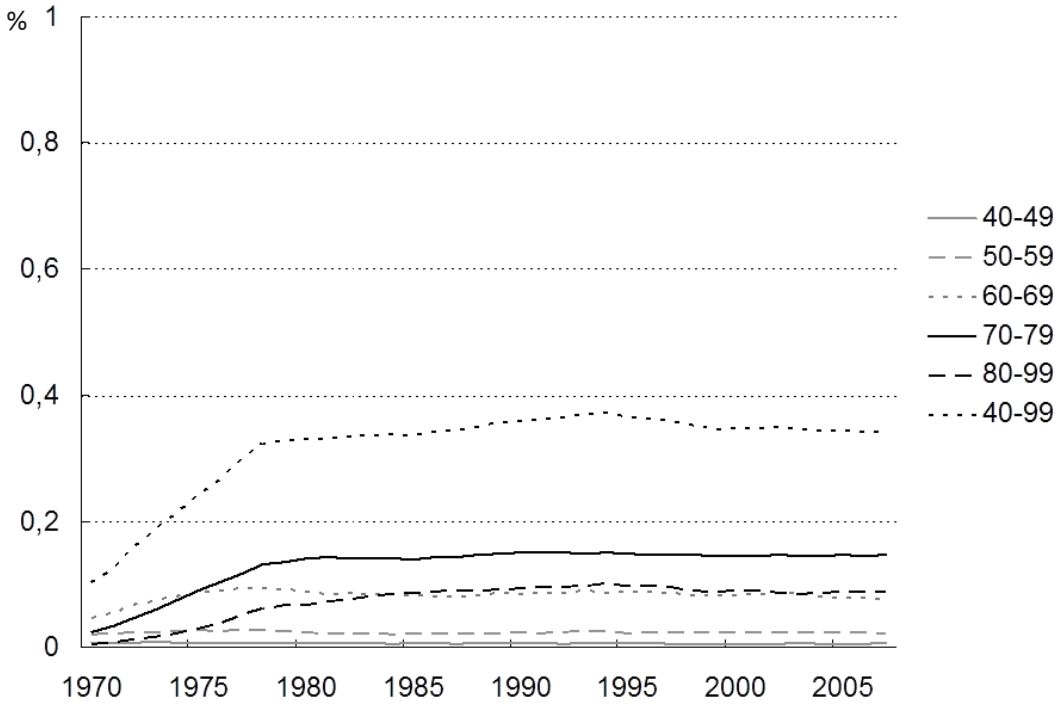

Figure 8. Age-adjusted prevalence of Parkinson's disease in **women** (excluding patients using antipsychotic medication) in the Finnish population (1970–2007) by age group, based on the Drug Reimbursement Register of the Social Insurance Institution.

4.3.2 Baseline exclusion criteria of prevalent PD for the cohort design

Follow-up information for the PD cases is based on the register information, as defined above (chapter 4.3.1). However, the baseline exclusion of prevalent PD cases was made by using both register information and survey data. Exclusion criteria at the baseline of the study cohorts are described in Table 17.

These exclusions were made to ensure the removal of all potential prevalent PD cases, since the non-motor symptoms of PD could, in some cases, include depression, mood disorders, and other psychiatric symptoms, as well as sleep disorders and cognitive impairment (see Kalia and Lang 2015a). Furthermore, we wanted to exclude drug-induced secondary parkinsonism potentially resulting from use of neuroleptic drugs. Thus, subjects with the reimbursement right codes 112 and 113 were also excluded.

Table 17. Baseline exclusion criteria for our study cohorts.

Finnish Mobile Clinic Health Examination Survey	Finnish Mobile Clinic Follow-up Survey	Mini-Finland Health Survey
i) subjects who had PD based on reimbursement right code110 within the SII's register, in addition to reimbursement right codes 112 (difficult psychosis and other difficult mental illnesses) and/or 113 (behavioral problems of the mentally retarded) ii) subjects who reported the use of parkinsonian medication or antipsychotic medication (according to Remedia Fennica 1975) iii) subjects who, at baseline questionnaire, reported suffering from mental illnesses or nervous disease at the time of baseline or before	i) same for all surveys ii) further extended to those reporting antidepressive/psycho-stimulating medication (according to Remedia Fennica 1975) iii) subjects who, at baseline questionnaire, reported being submitted to institutional care due to psychotic disorders at the time of baseline or before	i) same for all surveys ii) same as in the Finnish Mobile Clinic Follow-up Survey iii) same as in the Finnish Mobile Clinic Follow-up Survey

4.3.3 Evaluation of diagnostic accuracy

A sample of the certificates (n=126) for PD drug reimbursement were re-evaluated retrospectively against selected hospital records by our study neurologist, Jukka Lyytinen. The evaluation was made according to the National Institute of Neurological Disorders and Stroke's diagnostic criteria for PD (see Gelb et al. 1999).

Patient files were reviewed, paying special attention to evidence on factors that might contribute to the manifestations of parkinsonism (e.g. head trauma, infections of the central nervous system, cerebrovascular insults, psychiatric co-morbidity, or signs of other neurodegenerative diseases). Three categories were used to describe the clinical evidence supporting or refuting the presence of idiopathic PD. *Probable* meant that there was major evidence in support of idiopathic PD. *Possible* meant that there was some evidence in support of idiopathic PD, but the documentation, for example, was inadequate in describing the diagnostic criteria. *Unlikely* meant that there was enough evidence to refute idiopathic PD, for example the presence of one or more features that were considered as exclusion criteria.

Results of the re-evaluation of PD case records yielded 73% of patients classified as *probable* idiopathic PD, 7% as *possible* idiopathic PD, and 20% as *unlikely* to have idiopathic PD. Those classified as *unlikely* to have idiopathic PD had, for example, used dopamine antagonists in a time frame compatible with drug-induced parkinsonism, or had clinical "red flags" of atypical parkinsonism, such as pyramidal tract (motor paresis, hyperreflexia, positive Babinski sign), cerebellar (ataxia, nystagmus) or early prominent bulbar (dysphagia, gaze paresis) signs, or marked cognitive/postural/gait impairment at the time of diagnosis.

In conclusion, 80% of the originally identified PD cases in the register met the criteria [Jukka Lyytinen, personal communication, 2015, and Weisskopf et al. (2010)], which is consistent with other estimates of the percentage of people clinically diagnosed with PD in the general population that meet strict PD criteria (Schrag et al. 2002). Neuropathologic data to confirm the diagnosis as *definite* was not available in any of the cases.

4.3.4 Number of PD cases and length of follow-up in the sub-studies

An individual's follow-up time was defined as the number of days from the baseline examination to the date of PD occurrence, death, or withdrawal (i.e. end of follow-up), whichever came first. Table 18 shows the length of the follow-up periods and number of subjects identified as PD cases during this period for Studies I–IV.

Table 18. The length of follow-up and number of subjects in Studies I–IV.

Study	Baseline, year	End of follow-up, date	Maximal (and mean) follow-up time, years	No. at risk	No. of PD cases
I	1966–1972	31.12.2007	42 (19.4)	4,524	85
II	1973–1976	31.12.1994	22 (15.3)	6,715	101
III	1973–1976	31.12.1994	22 (15.3)	6,710	101
IV	1978–1980	31.12.2007	30 (22.6)	6,641	89

4.4 Statistical methods

Cox's proportional hazards model (Cox 1972) was used to estimate the strength of association between exposure variables (independent variable) (Table 19) and PD incidence (dependent variable), and the results were presented as relative risks with 95% confidence intervals. The significance of the associations was tested using the likelihood ratio test. Test for trend was performed by including continuous variables in the models.

Table 19. Classification of the exposure variables in Studies I–IV.

	Exposure variables
Study I	Tertiles of the consumption of individual food groups (g/d); Quartiles of the mAHEI scores
Study II	BMI (kg/m^2) = <23, 23–24.9, 25–27.4, 27.5–29.9, ≥30; Leisure-time physical activity = none, light, heavy; Smoking status = never, past, current; Alcohol consumption as ethanol (g/d) = 0, <5, ≥5
Study III	Coffee consumption (cups/d) = 0, 1–3, 4–9, ≥10
Study IV	BMI (kg/m^2) = <25, ≥25; Blood pressure = normal, elevated (SBP ≥130 mmHg or DBP ≥85 mmHg or antihypertensive drug treatment); Serum triglycerides (mmol/L) = <1.7, ≥1.7; Serum HDL cholesterol (mmol/L) = low (<1.3 mmol/L in women and <1.0 mmol/L in men), high (≥1.3 mmol/L in women and ≥1.0 mmol/L in men); Fasting plasma glucose (mmol/L) = <5.6, ≥5.6

The association between potential confounding factors and exposure variables, and confounding factors and PD, were studied using the general linear model. Statistical significance was tested with the F-test.

Confounding factors were selected from the literature, or identified by studying the background variables one by one; *P*-value <0.5 was the inclusion criteria for potential confounders. Potential confounding factors were adjusted for in the different multivariate models as described in the original articles (Studies I–IV) and in Table 20 on analyses strategy.

Potential effect-modifying factors were entered in the model as multiplicative interaction terms. In Study I, there were differences between men and women in the associations between diet and PD. The *P* for interaction was 0.08 when examining the association between mAHEI and PD. Thus, most of the analyses were stratified by sex in Study I.

Some of the potential effect-modifying factors included in the analyses were selected from the literature (e.g., sex, smoking, and BMI); some of them were exploratory in nature and were included without a predefined hypothesis (e.g., education, physical activity, and blood pressure). However, the number of PD cases proved to be too small for most of the interaction analyses, so we were able to report only a small part of these results.

In all studies, additional analyses excluding the first few years of follow-up were performed to examine the effect of the preclinical disease phase. Studies I and III included analyses with exclusion of the first 5 years of follow-up, which is commonly used as the exclusion time period when studying chronic diseases in prospective settings. However, we later decided to use a longer exclusion period, as PD could already begin decades before the onset of motor symptoms and diagnosis. Thus, in Studies II and IV, the effect of the preclinical disease phase was studied in more detail with analyses excluding the first 10 or 15 years of follow-up. For the purposes of this thesis, analyses excluding the first 10 or 15 years of the follow-up were also performed for Studies I and III, to complement those results. Furthermore, part of the published results was re-analyzed to present similar adjustments across the different studies (e.g. Studies II and III).

In addition, the short-term and long-term repeatability of the mAHEI was examined utilizing the intraclass correlation coefficient (Winer 1971), with mAHEI being measured as a continuous variable. Furthermore, the short-term repeatability of physical activity was examined with Kappa coefficients (Fleiss 1973), as physical activity was a categorized variable.

All analyses were carried out using SAS software, version 9 (SAS Institute Inc., Cary, NC, USA).

Table 20. Analysis strategy (for the original publications, unless otherwise stated).

Study I	Study II	Study III	Study IV
Confounding factors adjusted in the models			
model 1 = age (continuous), sex **model 2** = model 1 + marital status (unmarried; married; widow/er or divorced), urbanization (rural; urban or industrial), geographical area (South-West; South; Central; West; East; or North), smoking (never; quit ≥10 years ago; quit 1–9 years ago; quit <1 year ago; smokes only pipe or cigars; smokes <15 cigarettes/d; or smokes ≥15 cigarettes/d), BMI (<23; 23–24.9; 25–27.4; 27.5–29.9; or ≥30 kg/m^2), leisure-time physical activity (none; less than weekly; weekly or daily), and intake of energy (kJ/d) **model 3** = model 2 + hypertension (no; yes), serum total cholesterol (continuous; mmol/l), diabetes mellitus (no; yes), and, additionally, in women, parity (0; 1–3; or ≥4)	**model 1** = age (continuous), sex **model 2** = model 1 + education (1–9 years; ≥10 years), community density (rural; urban), occupation (classified in 12 categories according to the Nordic Classification of Occupations), coffee consumption (0; 1–3; 4–9; ≥10 cups/day), and all the main exposure variables, i.e., BMI (<23; 23–24.9; 25–27.4; 27.5–29.9; ≥30 kg/m^2), leisure-time physical activity (none; light; heavy), smoking status (never; past; current), and alcohol consumption as ethanol (0; <5; ≥5 g/day)	**model 1** = age (continuous), sex **model 2** [a] = model 1 + marital status (married; others), education (1–9; ≥10 years), community density (rural; urban), alcohol consumption as ethanol (0; <5; ≥5 g/d), leisure-time physical activity (none; light ≥4 h/week; heavy ≥3 h/week), smoking status (never/past; current), and BMI (<23; 23–24.9; 25–27.4; 27.5–29.9; ≥30 kg/m^2) **model 3** = model 2 + hypertension [yes; no (see (Knekt 1988) for description of categories)] and total serum cholesterol (quintiles)	**model 1** = age (continuous), sex **model 2** = model 1 + education (<7 years; 7–12 years; >12 years), smoking (never; former smoker; smokes only pipe or cigars or smokes <30 cigarettes/d; smokes ≥30 cigarettes/d), alcohol consumption as ethanol (0 g/week; 1–99 g/week for women and 1–199 g/week for men; ≥100 g/week for women and ≥200g/week for men), leisure-time physical activity (none; occasional; regular), vitamin D (median: <40 nmol/L; ≥40 nmol/L) and coffee consumption (0; 1–3; 4–9; ≥10 cups/d) **model 3** = model 2 + BMI (<25; ≥25 kg/m^2), blood pressure (normal; elevated SBP ≥130 mmHg or DBP ≥85 mmHg or antihypertensive drug treatment), serum triglycerides (normal; high ≥1.7 mmol/L), serum HDL cholesterol (normal; low <1.3 mmol/L in women and <1.0 mmol/L in men), fasting plasma glucose (normal; high ≥5.6 mmol/L)
Effect-modifying factors			
sex (further interaction analyses could not be performed due to the small number of PD cases)	age, sex, smoking, BMI, alcohol consumption, physical activity, coffee consumption	age, sex, education, smoking, BMI, alcohol consumption, physical activity, blood pressure, serum total cholesterol	interaction analyses could not be performed due to the small number of PD cases
Lag-analyses: years excluded from the beginning of the follow-up			
5[b]	10 and 15	5[b]	10
Secondary analyses			
-	-	-	shorter follow-up time (17 years) with the exclusion of the first 10 years of follow-up

[a] for this thesis analyses for model 2 included the same variables as in model 2 in Study II

[b] for this thesis also analyses with exclusion of 10 and 15 years were performed

4.5 Description of the baseline characteristics of the data

Table 21 briefly describes selected age- and sex-adjusted baseline characteristics of the FMC, FMCF and the Mini-Finland Health Survey. Factors that were comparable between the surveys were chosen.

The associations between baseline characteristics and PD incidence, and between baseline characteristics and exposure factors, were studied to identify potential confounding factors and are described in detail in the original articles (Studies I–IV).

In the FMC (Study I), 13.5% of PD cases were smokers, while 31.5% of subjects who were free from PD smoked (P<0.001). PD was not notably associated with any other background variable in the FMC. In the FMCF (Studies II and III), subjects who developed PD during the follow-up were older, were more often non-smokers, and consumed less coffee than those without PD (P<0.05). In the Mini-Finland Health Survey (Study IV), those who subsequently developed PD were older, more often non-smokers, had lower serum vitamin D, serum triglyceride, and fasting plasma glucose concentrations, and were less likely to have metabolic syndrome than subjects who were free of the disease (P<0.04).

Furthermore, several background variables were associated with the diet quality scores in the FMC (Study I). Subjects who were in the highest quartile of the mAHEI were typically younger and married, and they had a higher BMI and serum total cholesterol level than subjects in the lowest quartile (P<0.05). They were also less likely to live in rural areas and to smoke, and more likely to take part in leisure-time physical activities then subjects in the lowest quartile of the mAHEI (P<0.05).

In the FMCF (Studies II and III), BMI was associated with most of the background variables (P<0.01), but not with coffee or alcohol consumption. Leisure-time physical activity, in turn, was associated with all of the other background variables (P<0.01), except alcohol consumption. Men smoked and took part in heavy leisure-time physical activities more than women (P<0.001). Furthermore, smoking was associated with all of the background variables examined (P<0.002), except community density. Alcohol consumption was also associated with all of the background variables (P<0.01), but not with BMI. Subjects who did not drink alcohol were older and more often women (P<0.001). Coffee consumption was associated with all of the background variables (P<0.04), except BMI.

In the Mini-Finland Health Survey (Study IV), the mean values and percentages for individual characteristics varied by categories of metabolic syndrome and its components. Subjects who had metabolic syndrome were more likely to be older, men, less educated, to practice less leisure-time physical activity, and to have a lower concentration of serum vitamin D. Furthermore, subjects who had a serum total cholesterol concentration above 5.0 mmol/L were more likely to be older, drink more coffee, and have a higher serum vitamin D concentration.

Table 21. Age- and sex-adjusted baseline characteristics in incident cases of PD and in subjects free from PD.

	Finnish Mobile Clinic Health Examination Survey (1966–1972) (Study I)		Finnish Mobile Clinic Follow-up Survey (1973–1976) (Studies II and III[a])		Mini-Finland Health Survey (1978–1980) (Study IV)	
	PD cases	Subjects free from PD	PD cases	Subjects free from PD	PD cases	Subjects free from PD
N	85	4,439	101	6,614	89	6,552
Age (years, mean)[b]	52.2	53.3	62.7	60.7	56.5	50.2
Males (%)[c]	52.6	52.8	45.2	47.6	54.6	46.6
Education, ≥7 years (%)	-	-	21.7	19.0	36.1	33.2
Married (%)	69.5	76.7	68.0	69.2	77.7	73.1
Community density, rural (%)	34.6	38.8	33.4	36.9	38.6	37.5
Current smokers (%)	13.5	31.5	6.1	21.8	9.0	24.1
Alcohol consumption (g/d, mean)						
Male	-	-	5.8	7.1	7.9	12.2
Female	-	-	0.5	0.6	2.3	2.0
Coffee consumption (cups/d, mean)	-	-	5.0	5.5	5.0	5.2
BMI (kg/m^2, mean)	27.0	26.5	27.4	26.7	26.2	25.8
Leisure-time physical activity, none (%)	52.9[d]	54.6[d]	31.5[e]	28.3[e]	27.1[f]	34.5[f]

Abbreviations: PD, Parkinson's disease; g, gram; d, day; BMI, body mass index.
[a] 5 subjects with missing information on coffee consumption were excluded in Study III, but this did not substantially change the mean values and distributions of the baseline characteristics, so the results, with n=6,715, are shown here
[b] adjusted for sex
[c] adjusted for age
[d] specific category response: less than weekly
[e] specific category response: none (during a typical week)
[f] specific category response: none (main leisure time activities do not include physical strain but e.g. reading and watching television)

5 Results

5.1 Food consumption, quality of diet, and the risk of PD (Study I)

Most of the individual food groups or items examined had no statistically significant association with the risk of PD in model 3, in men or women (Figures 9 and 10). However, in men, the risk of PD was statistically significantly increased when the intake of fruits and berries was compared between the highest and lowest tertiles (RR 3.67, 95% CI 1.30–10.36, *P* for trend 0.60, model 3). The increased PD risk was also observed when the intake of fresh fruits was compared between the highest and lowest tertiles (RR 2.41, 95% CI 1.01–5.77, *P* for trend 0.48, model 3). However, after exclusion of the first 10 years of follow-up, these associations were no longer statistically significant (the corresponding RR being 2.71, 95% CI 0.93–8.00, *P* for trend 0.83 for the consumption of fruits and berries, and 1.63, 95% CI 0.64–4.10, *P* for trend 0.61 for fresh fruits) (Sääksjärvi et al. unpublished results).

Women in the highest tertile for the consumption of milk had a statistically significantly higher risk of PD compared with women in the lowest tertile (RR 3.31, 95% CI 1.10–9.93, *P* for trend 0.09, model 3). Furthermore, there was a statistically significant inverse trend for berries (highest v. lowest tertile, RR 0.54, 95% CI 0.23–1.27, *P* for trend 0.02, model 3) among women. In addition, a statistically significant inverse association was observed between the consumption of processed meat and sausages and the incidence of PD in women, with the RR of developing the disease between the highest and lowest tertiles being 0.39 (95% CI 0.16–0.95, *P* for trend.0.008, model 3). The exclusion of the first 10 years of follow-up did not notably change the results for the consumption of milk (RR 3.41, 95% CI 1.13–10.29, *P* for trend 0.06), or berries (corresponding RR being 0.58, 95% CI 0.25–1.39, *P* for trend 0.04), or processed meat and sausages (RR 0.45, 95% CI 0.18–1.10, *P* for trend 0.01) (Sääksjärvi et al. unpublished results).

Diet quality, defined by the mAHEI, did not predict PD incidence (Table 22). The RR between the highest and lowest quartiles of the mAHEI was 1.83 (95% CI 0.65–5.18, *P* for trend 0.11) in men and 0.97 (95% CI 0.38–2.48, *P* for trend 0.91) in model 3.

Excluding the first 5 years of follow-up did not notably alter the results concerning the individual food groups or the diet quality index (data not shown). For the mAHEI, further analyses excluding the first 10 years of follow-up did not substantially change the results either, the corresponding RRs being 1.10 for men (95% CI 0.42–2.88, *P* for trend 0.16) and 1.00 for women (95% CI 0.38–2.63, *P* for trend 0.92) (Sääksjärvi et al. unpublished results). The exclusion of the first 10 years of follow-up decreased the number of PD cases from 40 to 38 in women, and from 45 to 38 in men.

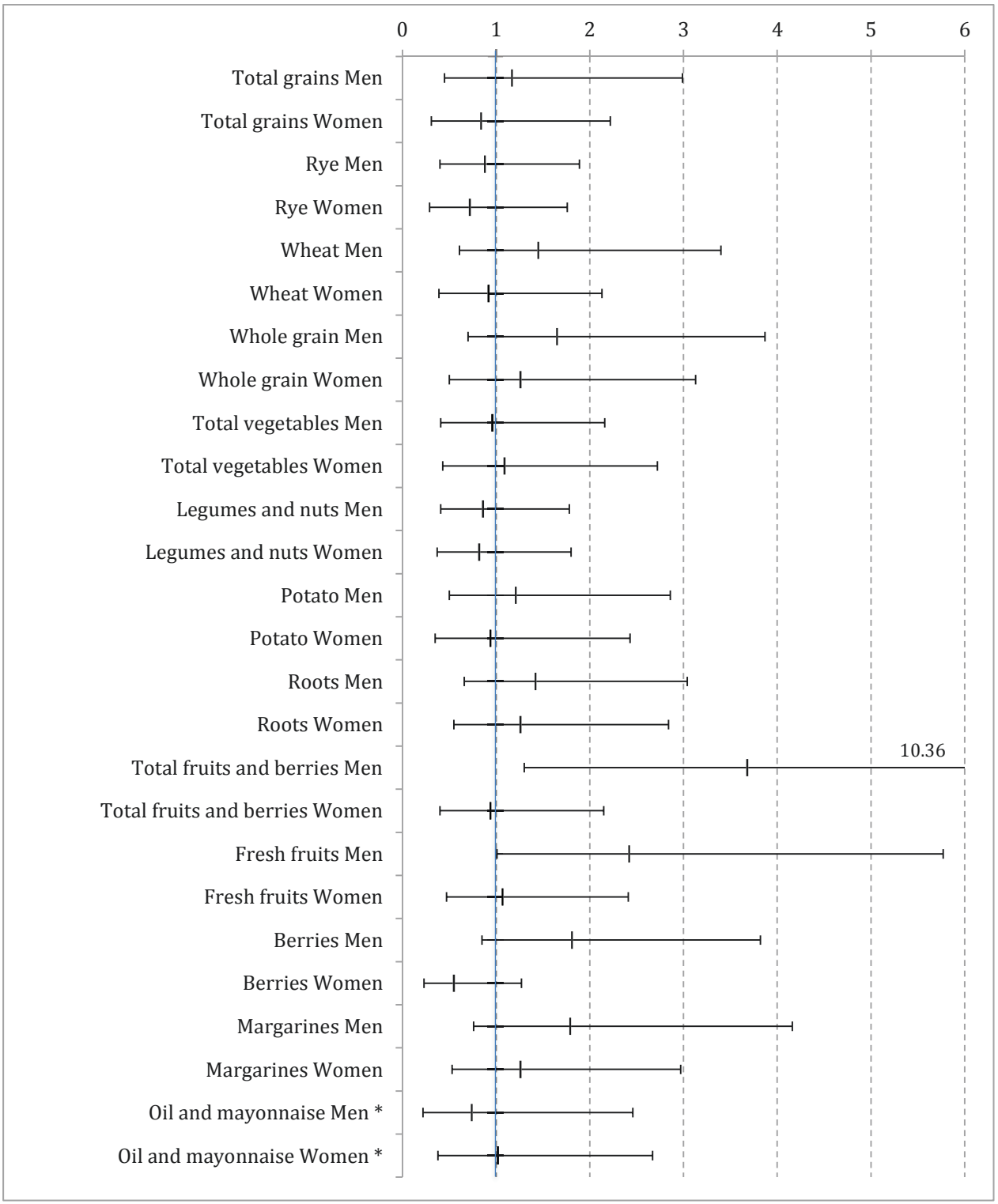

Figure 9. The relative risks and their 95% confidence intervals for Parkinson's disease comparing the highest versus lowest tertile of consumption of individual food groups or items from the Finnish Mobile Clinic Health Examination Survey, 1966–1972. Adjusted for age, sex, marital status, community density, geographical area, smoking, BMI, leisure-time physical activity, energy intake, hypertension, serum total cholesterol, diabetes and, in addition, in women, parity. *Compares median classes since distribution did not allow classification into tertiles.

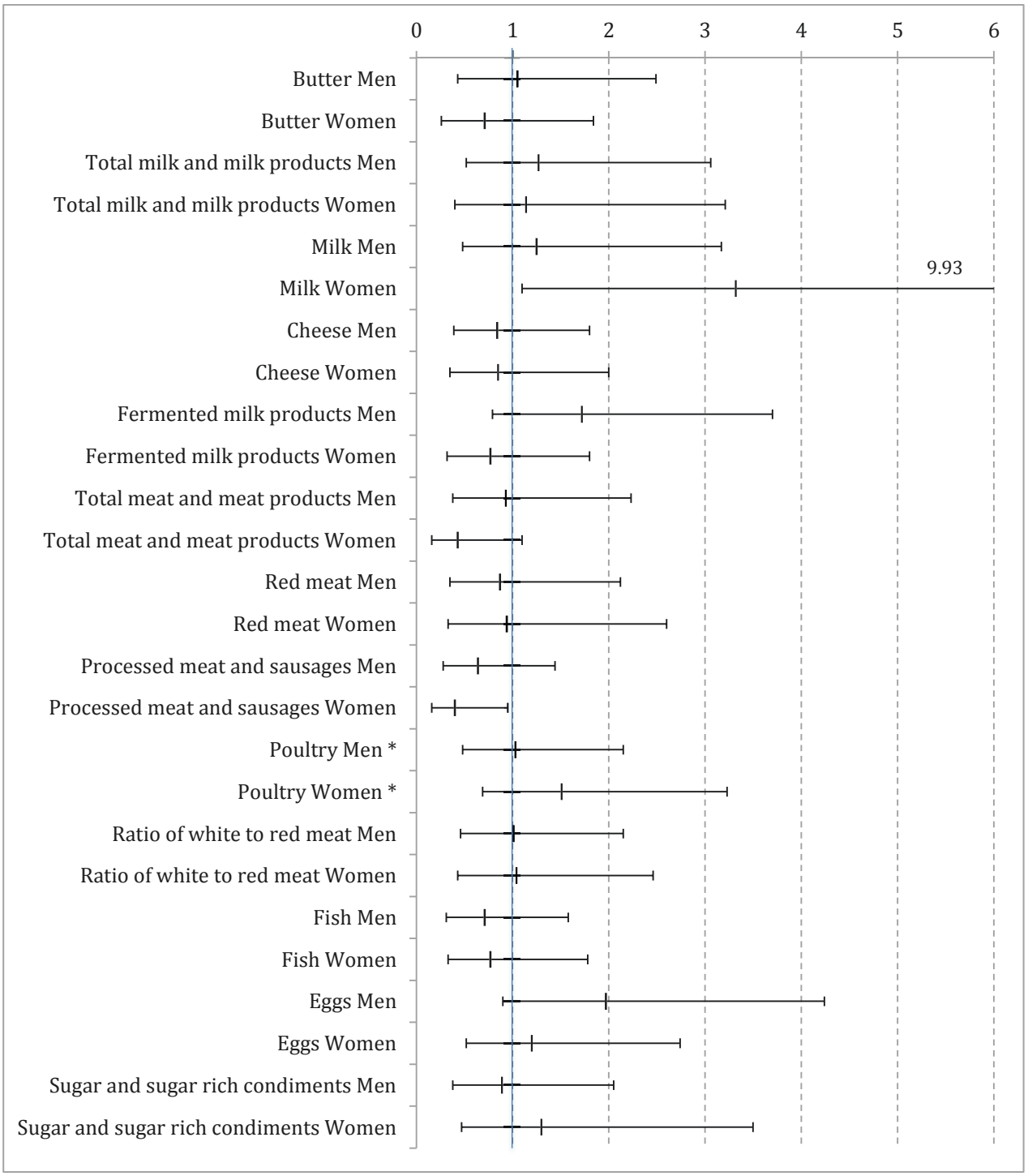

Figure 10. The relative risks and their 95% confidence intervals for Parkinson's disease comparing the highest versus lowest tertile of consumption of individual food groups or items from the Finnish Mobile Clinic Health Examination Survey, 1966–1972. Adjusted for age, sex, marital status, community density, geographical area, smoking, BMI, leisure-time physical activity, energy intake, hypertension, serum total cholesterol, diabetes and, in addition, in women, parity. *Compares median classes since distribution did not allow classification into tertiles.

Table 22. Multivariate-adjusted relative risks and their 95% confidence intervals of Parkinson's disease by quartiles of the modified Alternate Healthy Eating Index, the Finnish Mobile Clinic Health Examination Survey, 1966–1972.

	Diet quality index, quartiles[a]				
	Q1	Q2	Q3	Q4	*P* for trend
Men					
Age-adjusted model					0.18
n/N	8/689	12/592	15/583	10/524	
RR	1.00	1.68	2.06	1.46	
95% CI	-	0.69–4.12	0.87–4.87	0.58–3.71	
model 2[b]					0.13
n/N	8/684	12/584	15/576	10/519	
RR	1.00	1.85	2.53	1.73	
95% CI	-	0.71–4.79	0.98–6.52	0.61–4.88	
model 3[c]					0.11
n/N	8/684	12/584	15/576	10/519	
RR	1.00	2.00	2.52	1.83	
95% CI	-	0.77–5.22	0.97–6.55	0.65–5.18	
Women					
Age-adjusted model					0.95
n/N	10/572	14/565	6/522	10/477	
RR	1.00	1.36	0.58	1.03	
95% CI	-	0.60–3.08	0.21–1.61	0.42–2.48	
model 2[b]					
n/N	10/569	14/559	6/519	10/474	0.85
RR	1.00	1.32	0.57	1.01	
95% CI	-	0.57–3.09	0.20–1.63	0.40–2.54	
model 3[c]					0.91
n/N	10/563	14/553	6/516	10/471	
RR	1.00	1.27	0.54	0.97	
95% CI	-	0.54–2.99	0.19–1.55	0.38–2.48	

Abbreviations: n, Parkinson's disease cases; N, total population; RR, relative risk; CI, confidence interval

[a] cut˙off points of quartiles are, for men, 7–18, 19–21, 22–24, 25–34; and for women, 8–18, 19–21, 22–24, 25–34

[b] adjusted for age, sex, marital status, community density, geographical area, smoking, BMI, leisure-time physical activity, energy

[c] adjusted for all of the factors in model 2 plus hypertension, serum cholesterol, diabetes mellitus (in addition, in women: parity)

5.2 Lifestyle factors and the risk of PD (Studies II and III)

Higher leisure-time physical activity was statistically significantly associated with a lower risk of PD (RR 0.27, 95% CI 0.08–0.90, for subjects having heavy physical activity compared to those who had none, *P* for heterogeneity 0.04) in model 2 (Table 23). However, the association between leisure-time physical activity and PD risk attenuated when analyses excluding the first 10 or 15 years of follow-up were performed.

The interaction analyses revealed an inverse association between physical activity and PD risk that was stronger in a few subgroups. A statistically significant inverse association with PD risk was seen in women (RR 0.49, 95% CI 0.28–0.85) (*P* for interaction 0.06), in subjects with a BMI ≥27.5 (RR 0.55, 95% CI 0.31–0.99) (*P* for interaction 0.008), and in subjects drinking <3 cups of coffee per day (RR 0.42, 95% CI 0.20–0.88) (*P* for interaction 0.12), when comparing those who engaged in any leisure-time physical activity to those who engaged in none. Possible effect modification of smoking could not be examined due to the small number of subjects.

We found a statistically significant inverse association between smoking and PD (Table 23). The RR for current smokers compared to those who had never smoked was 0.23 (95% CI 0.08–0.67, *P* for heterogeneity 0.001) in model 2. The risk of PD was not reduced, however, for past smokers when compared to those who had never smoked. Furthermore, the statistically significant inverse association between smoking and PD risk persisted when the first 10 years of follow-up were excluded from the analyses. After the first 15 years of follow-up were excluded, however, while the point estimate did not change, the association was no longer statistically significant (RR 0.19, 95% CI 0.02–1.60, current smokers v. never smokers, *P* for heterogeneity 0.09). Interaction analyses could not be performed due to the small number of PD cases.

Furthermore, we found that subjects who consumed <5g of alcohol per day had a higher risk of PD compared to non-drinkers (RR 1.81, 95% CI 1.12–2.93, *P* for trend 0.30, *P* for heterogeneity 0.02) in model 2 (Table 23). This elevated risk of PD persisted after the exclusion of the first 10 (RR 1.94, 95% CI 1.09–3.47, *P* for heterogeneity 0.07) and 15 years of follow-up (RR 2.66, 95% CI 1.07–6.62, *P* for heterogeneity 0.11), although no trend appeared (*P* for trend 0.37 after the exclusion of 10 years and 0.89 after 15 years).

However, analyses restricted to alcohol consumers revealed that subjects who consumed ≥5g of alcohol per day had a lower risk of PD compared to those who consumed <5g of alcohol per day, the RR being 0.52 (95% CI 0.26–1.06, *P* for trend 0.11), although the association was not statistically significant (model 2). This suggestive inverse association was slightly attenuated after excluding the first 10 years of follow-up (*P* for trend 0.11) and disappeared after excluding the first 15 years (*P* for trend 0.53).

Regarding the association between alcohol consumption and PD risk, no interactions were observed. However, the effect modification by sex could not be examined due to the small number of PD cases.

Finally, subjects who consumed at least 10 cups of coffee per day had a lower PD risk compared to non-drinkers (RR 0.24, 95% CI 0.06–0.92, *P* for trend 0.11) in model 2. Further interaction analyses revealed that the statistically significant inverse association was present among overweight subjects (that is, BMI $\geq$25 kg/m^2) (*P* for interaction 0.04), and among subjects who had serum cholesterol levels under the median (<7.24 mmol/l) (*P* for interaction 0.03)(see Study III, Table 4). Furthermore, although the interaction was not statistically significant for any other variable examined as an effect-modifying factor, the inverse association was present for those who were younger (aged 50–69 years), had lower education, had no leisure-time physical activity, and had no hypertension.

The inverse association between coffee consumption and PD risk attenuated after exclusion of the first 10 and 15 years of follow-up (*P* for trend 0.21 and 0.30, respectively) (Sääksjärvi et al. unpublished results). However, when subjects drinking at least four cups of coffee per day were compared to subjects drinking 0–3 cups per day, the statistically significant inverse association persisted (RR 0.59, 95% CI 0.35–0.99, *P* for heterogeneity 0.06) even after excluding the first 10 years of follow-up, but not after exclusion of 15 years (RR 0.68, 95% CI 0.29–1.56, *P* for heterogeneity 0.37) (Sääksjärvi et al. unpublished results).

In the FMCF, regarding the analyses on leisure-time physical activity, smoking, alcohol consumption, and coffee consumption, the number of PD cases was 66 after excluding the first 10 years of follow-up, and 28 after 15 years.

Table 23. Multivariate-adjusted relative risks and their 95% confidence intervals of Parkinson's disease by leisure-time physical activity, smoking, alcohol and coffee consumption, the Finnish Mobile Clinic Follow-up Survey, 1973–1976.

	Complete model[a, b]				First 10 years of follow-up excluded[b]			
	n/N	RR	95% CI	*P*[c]	n/N	RR	95% CI	*P*[c]
Leisure-time physical activity				0.04				0.06
none	32/1,854	1.00	-		23/1,366	1.00	-	
light	62/4,190	0.73	0.47–1.13		41/3,280	0.65	0.38–1.10	
heavy, ≥ 3 h/week	3/472	0.27	0.08–0.90		2/401	0.25	0.06–1.09	
Smoking status				0.001				0.004
never	66/3,820	1.00	-		45/3,130	1.00	-	
past smoker	27/1,291	1.17	0.66–2.09		19/963	1.42	0.70–2.88	
current smoker	4/1,405	0.23	0.08–0.67		2/954	0.20	0.04–0.88	
Alcohol consumption (g/d)[d]				0.02				0.07
0	50/3,515	1.00	-		33/2,757	1.00	-	
<5	35/1,747	1.81	1.12–2.93		24/1,373	1.94	1.09–3.47	
≥5	12/1,254	0.91	0.44–1.89		9/917	1.12	0.47–2.69	
Coffee consumption (cups/d)				0.11[e]				0.21[e]
0	8/320	1.00	-		4/243	1.00	-	
1–3	21/983	0.86	0.38–1.96		17/728	1.33	0.44–4.00	
4–9	65/4,557	0.60	0.28–1.26		42/3,555	0.76	0.27–2.14	
≥10	3/656	0.24	0.06–0.92		3/521	0.48	0.11–2.19	

Abbreviations: n, Parkinson's disease cases; N, total population; RR, relative risk; CI, confidence intervals; h, hour; g, gram; d, day.
[a] Total follow-up
[b] Adjusted for age, sex, education, community density, occupation, leisure-time physical activity, smoking, alcohol consumption, coffee consumption, and body mass index
[c] *P* for heterogeneity, unless otherwise indicated
[d] Alcohol consumption as ethanol g/d
[e] *P* for trend

5.3 Obesity, metabolic health, and the risk of PD (Studies II and IV)

Body mass index was studied in both the FMCF (Study II) and the Mini-Finland Health Survey (Study IV). In both studies, no statistically significant association was found between BMI and PD risk in the crude or multivariate models (Table 24). However, a positive association between BMI and PD risk appeared in the FMCF after excluding the first 15 years of follow-up (*P* for trend 0.02 in model 2).

In the Mini-Finland Health Survey, after excluding the first 10 years of follow-up, it seemed that subjects with a BMI over 25 had an increased PD risk compared to those with normal weight (RR 1.75, 95% CI 1.00–3.07). After further applying a shorter, 17-years, follow-up time, a dose-response relationship was revealed (*P* for trend 0.06 in model 3).

In Study II, no effect modification by age, sex, smoking, alcohol consumption, or coffee consumption could be found before exclusion of the first 15 years of follow-up. Additionally, after the exclusion, the number of PD cases was too small for interaction analyses.

The results for other variables on metabolic health are shown in Table 24, and were studied only in the Mini-Finland Health Survey, where data was available.

The relative risk of PD in subjects with metabolic syndrome compared to those without was 0.50 (95% CI 0.30–0.83) in model 2 (Table 24). Exclusion of the first 10 years of follow-up did not change this result (Table 24) (unpublished result Sääksjärvi et al.). Furthermore, applying a shorter follow-up time did not change the result either (data not shown). However, further analyses revealed that the association between metabolic syndrome and PD incidence was not statistically significant if serum triglycerides were removed from the definition of metabolic syndrome and included as an adjusting factor in the model (data not shown).

When examining the individual components of metabolic syndrome, a statistically significantly reduced risk of PD was observed when subjects with elevated serum triglyceride concentration were compared to those with normal concentration (RR 0.52, 95% CI 0.30–0.89, *P* for trend 0.02, model 2) (Table 24). A statistically significant inverse association between serum triglyceride concentration and PD incidence remained after further adjusting for other components of metabolic syndrome (*P* for trend 0.02), and strengthened after excluding the first 10 years of follow-up (*P* for trend 0.01) (Table 24). Applying the shorter follow-up time did not change the results (data not shown).

A statistically significantly reduced risk of PD was also seen when subjects with elevated fasting plasma glucose concentration were compared to those with normal concentration (RR 0.56, 95% CI 0.32–0.98, *P* for trend 0.05, model 2) (Table 24). The association weakened slightly after further adjusting for other components of metabolic syndrome (*P* for trend 0.08). Furthermore, after excluding the first 10 years of follow-up, the trend was no longer statistically significant (*P* for trend 0.19 in model 3), however, elevated glucose concentration still predicted a reduced PD risk (RR 0.47, 95% CI 0.23–0.97). Finally, applying a shorter follow-up time did not change the results (data not shown).

The risk of PD was not statistically significantly associated with blood pressure, serum HDL cholesterol, or serum total cholesterol concentration in the crude or multivariate models. Neither further adjustments nor exclusion of the first 10 years of follow-up changed the results. Furthermore, applying the shorter follow-up time did not change the results (data not shown).

Table 24. Multivariate-adjusted relative risks and their 95% confidence intervals of Parkinson's disease between categories of metabolic factors.

Variable	n/N	RR	95% CI	*P* for trend	n/N	RR	95% CI	*P* for trend
Finnish Mobile Clinic Follow-up Survey, 1973–1976	Total follow-up[a]				First 15 years of follow-up excluded[a]			
BMI (kg/m^2)				0.33				0.02
<25	29/2,329	1.00	-		6/1,419	1.00	-	
≥25	68/4,187	1.10	0.71–1.72		22/2,679	1.77	0.71–4.42	
Mini-Finland Health Survey, 1978–1980	Total follow-up[b]				First 10 years of follow-up excluded[c]			
BMI (kg/m^2)				0.98				0.22
<25	29/2,980	1.00	-		19/2,623	1.00	-	
≥25	57/3,508	1.18	0.75–1.87		44/3,010	1.75	1.00–3.07	
Blood pressure[d]				-				-
Normal	11/1,382	1.00	-		11/1,324	1.00	-	
Elevated	75/5,108	1.07	0.55–2.07		52/4,309	0.92	0.46–1.82	
Serum triglycerides (mmol/L)				0.02				0.01
<1.7	69/4,670	1.00	-		53/4,188	1.00	-	
≥1.7	17/1,821	0.52	0.30–0.89		10/1,445	0.43	0.21–0.86	
Serum HDL cholesterol (mmol/L)[e]				0.97				0.10
High	83/6,085	1.00	-		62/5,331	1.00	-	
Low	3/403	0.56	0.17–1.79		1/302	0.39	0.05–2.90	
Fasting plasma glucose (mmol/L)				0.05				0.19
<5.6	70/4,863	1.00	-		54/4,373	1.00	-	
≥5.6	16/1,628	0.56	0.32–0.98		9/1,260	0.47	0.23–0.97	
Metabolic syndrome[f]				-				-
Negative	66/4,497	1.00	-		52/4,054	1.00	-	[b]
Positive	20/1,994	0.50	0.30–0.83		11/1,583	0.37	0.19–0.73	[b]
Serum total cholesterol (mmol/L)				0.50				0.67
<5	4/373	1.00	-		4/334	1.00	-	
≥5	82/6,118	0.85	0.31–2.33		59/5,299	0.68	0.24–1.92	

Abbreviations: n, Parkinson's disease cases; N, total population; RR, relative risk; CI, confidence intervals; BMI, body mass index; HDL, high density lipoprotein

[a] Adjusted for age, sex, education, community density, occupation, leisure-time physical activity, smoking, alcohol consumption, and coffee consumption

[b] Adjusted for age, sex, education, smoking, alcohol consumption, leisure-time physical activity, serum vitamin D, and coffee consumption (model indicated with gray color in the table)

[c] Adjustments as in [b] plus additional adjustments for BMI, blood pressure, serum triglycerides, serum HDL cholesterol, and fasting plasma glucose, unless otherwise indicated

[d] Elevated: systolic blood pressure (SBP) ≥130 mmHg or diastolic blood pressure (DBP) ≥85 mmHg or antihypertensive drug treatment. Normal: Not elevated

[e] High: ≥1.3 mmol/L in women and ≥1.0 mmol/L in men. Low: <1.3 mmol/L in women and <1.0 mmol/L in men

[f] Defined as presence of any 3 or more of the following 5 risk factors: BMI ≥25 kg/m^2, SBP ≥130 mmHg or DBP ≥85 mmHg or antihypertensive drug treatment, serum triglycerides ≥1.7 mmol/L, serum HDL cholesterol <1.3 mmol/L in women and <1.0 mmol/L in men, and fasting plasma glucose ≥5.6 mmol/L

6 Discussion

6.1 Food consumption, overall quality of diet, and the risk of PD (Study I)

In general, most of the individual food groups or items examined did not predict the incidence of PD in the current study. A few food items, however, were found to be associated with the risk of disease.

Milk and dairy products

In this study, a positive association between milk consumption and PD incidence was found in women. Women who consumed more than 3.5 cups (6.1 dl) of milk per day, compared to those who consumed less than 2 cups (3.7 dl), had 3.3 times higher risk of PD. Four other cohort studies have also found a positive association between milk consumption and PD risk (Kyrozis et al. 2013; Chen et al. 2007; Park et al. 2005; Chen et al. 2002). However, one of the studies found a positive association in men only, not women (Chen et al. 2002), whereas another study included only men (Park et al. 2005). Nevertheless, two of the studies, from the United States and Greece (Kyrozis et al. 2013; Chen et al. 2007), found a higher PD risk among milk consumers in both men and women. The lack of association among men in this study could be attributed to the different intake levels of milk for men and women. Although men consumed more milk than women, they had a rather narrow range of intake (Appendix table 2). Thus, it could be that the differences between the intakes were not large enough to observe any association in men.

It is not clear whether nutrients or other constituents in milk would mediate this positive association between PD risk and milk consumption. However, a large cohort study of men and women from the United States concluded that it is unlikely to be due to calcium, vitamin D, or fat, as they did not have a positive association with PD risk when derived from sources other than dairy products (Chen et al. 2007). Regarding milk fat, this suggestion is supported in the present study, as high intake of reduced-fat dairy was also associated with increased PD risk (RR 2.69, 95% CI 1.08–6.66, comparing upper median class against lower median class). One possible explanation is that milk protein intake decreases the circulating levels of uric acid (Garrel et al. 1991), thus contributing to higher PD risk, as uric acid has been inversely associated with PD risk (Weisskopf et al. 2007; de Lau et al. 2005b; Davis et al. 1996). Another possibility is that dairy products are contaminated with neurotoxins due to their exposure to pesticides during farming, which may increase the risk of PD (see Priyadarshi et al. 2000).

It remains unclear why only milk consumption had a positive association with PD in this study but not consumption of other dairy products. However, our finding is in line with two previous cohort studies observing the positive association only for milk consumption and not for other types of dairy products (Kyrozis et al. 2013; Chen et al. 2007).

Meat, meat products, poultry, and fish

An inverse association between the intake of processed meat and sausages and PD incidence was observed for women but not for men in this study. Women who consumed more than 35 g/d of processed meat and sausages had a 41% lower risk of PD than women consuming less than 13 g/d. However, no associations were observed for consumption of total meat, red meat, poultry, or fish in either men or women.

The number of previous cohort studies on diet and PD risk is sparse, and their results have been inconsistent regarding the association between PD risk and the consumption of different meats, or the

intake of protein or iron, as described in the review by Ishihara and Brayne (2005). Only three cohort studies have examined the association between meat consumption and PD risk. In line with our findings, a nested case-control study from China found an inverse association between total meat consumption and PD risk. This study, however, was conducted in a region known for persistent dietary nutritional deficiencies. As no adjustments for caloric intake were applied, the result may reflect more the general nutritional status than meat consumption alone.

A large cohort study conducted in the United States found no associations for the consumption of total meat, red meat, poultry, or fish, in either men or women (Chen et al. 2002). Similarly, the EPIC-Greece cohort study did not find an association between PD risk and the consumption of meat and meat products, or fish (Kyrozis et al. 2013), but they reported results for men and women together.

The biological mechanism behind the inverse association between meat consumption and PD risk remains unclear. However, meat is a source of niacin, a vitamin reported to be inversely associated with PD and hypothesized to act via mechanisms related to nicotinamide metabolism (Hellenbrand et al. 1996). Another hypothesis regards the inverse association between uric acid and PD risk, as meat products are a rich source of animal proteins, which, in turn, contributes to higher uric acid levels (see Chaudhary et al. 2013). However, despite these hypotheses, it is unconvincing that only the consumption of processed meat and sausages would protect from PD and not red meat. Thus, the possibility of a chance finding must be considered.

Fruits, berries, and vegetables

Somewhat contrasting results between women and men were found for the consumption of fruit and berries. An inverse association between the consumption of berries and the risk of PD was found in women, but not in men. On the other hand, a high consumption of fruits and berries, and fresh fruits, was associated with an increased PD risk in men, a finding not seen in women. Furthermore, the consumption of vegetables was not associated with the risk of developing the disease in either women or men.

The present results do not support the prevailing hypothesis that the consumption of fruits and vegetables containing antioxidative substances would protect against the presumed oxidative stress in the pathogenesis of PD. The evidence from previous epidemiological studies is also inconclusive, showing mainly no association between the consumption of fruits and vegetables, or intakes of antioxidant vitamins, and PD risk (see Gaenslen et al. 2008; see Ishihara and Brayne 2005). One alternative explanation is that the use of pesticides in farming may increase the risk of PD, thus masking the potential benefit of consuming fruits and vegetables. Furthermore, a reason why berries but not fruits were inversely associated with PD incidence (in women) could be that the use of pesticides does not have an effect on berries gathered from nature, a typical source of berries in Finland. However, the pesticide hypothesis is also rather questionable, as a nested case–control study based on this same data (FMC) did not find strong evidence for an increased risk of PD due to pesticide exposure (Weisskopf et al. 2010).

Furthermore, the intake levels of fruits and berries were rather low in this study (Appendix table 2). It is possible that the inverse association between berry consumption and PD risk observed here could disappear at higher intake levels, reflecting the optimal intake level of this food item. However, there are no previous prospective studies examining the consumption of berries and PD risk to compare with.

Multiple comparisons

It should be noted that our study on individual food groups and items and the risk of PD included multiple comparisons, which increase the likelihood of a chance finding. The study included 52 significance tests; thus, after applying the Bonferroni correction at a significance level of 5%, we should consider each individual hypothesis to be statistically significant if the *P*-value is <0.001. After this correction, none of the food items studied was statistically significantly associated with PD risk. However, it could be argued that the positive association between the consumption of milk and PD risk is not just a chance finding, as similar results have been found in several previous cohort studies (Kyrozis et al. 2013; Chen et al. 2007; Park et al. 2005; Chen et al. 2002), although no plausible biological mechanism exists. Regarding the other findings on individual food items (i.e. processed meat and sausages, fruits and berries, berries, and fresh fruits), the possibility of a chance finding due to multiple comparisons is a concern and must be considered as a limitation to this study.

The diet quality index

The mAHEI, an index measuring adherence to a recommended diet, did not predict PD incidence in the present study. This is in contrast with the only other previous cohort study on diet quality and PD risk, which reported a reduction in PD risk with increasing diet quality as defined by the AHEI among the participants of the Nurses' Health Study and the Health Professionals Follow-up Study (Gao et al. 2007). However, in the present study, the lack of association between mAHEI and PD risk is in agreement with the fact that PD was also not associated with the components that make up the mAHEI, or with most of the food items examined here. The lack of association in our study could be due to a smaller study size, or due to different intake levels of food items. Additionally, the AHEI might be better suited to the diet common in the United States rather than Finland.

On the other hand, it is possible that the finding by Gao et al. (2007) could be explained by some unknown confounding factor associated with adhering to dietary guidelines that was not present in our study. This question emerges, as previous observations from the same cohort Gao used did not find association between PD risk and consumption of white meat (fish and poultry), fruits, or vegetables (Chen et al. 2002), which are key components of the AHEI. However, previous results from that cohort showed a possible adverse effect of saturated fat for men (Chen et al. 2003), and a beneficial effect of beer consumption for both genders (Hernan et al. 2003). Saturated fat and alcohol consumption were also components of the AHEI, and these findings agree with the observation by Gao et al. (2007) regarding the inverse association of the AHEI with PD risk.

Nevertheless, it seems that the mAHEI we used is a good tool for assessing diet quality, since it was inversely associated with the incidence of coronary heart disease in the present study population (Sääksjärvi et al. 2015). Furthermore, the dietary data collected in the FMC appears to be of good quality, as studies based on this dietary data have given consistent findings on the associations with several chronic diseases, such as coronary heart disease (Knekt et al. 1996), type 2 diabetes (Montonen et al. 2005), and stroke (Mizrahi et al. 2009). Furthermore, the reproducibility of the dietary history method used has been examined, and was found to be acceptable (Järvinen et al. 1993).

Effect modification

In the present study, an effect modification of sex was observed. For example, for increasing diet quality scores men had point estimates above unity, whereas women had point estimates mostly below unity; the

P-value for the interaction term being 0.08. Similarly, the results for individual food groups and items showed point estimates in the opposite direction for men and women for several variables (see Figures 9 and 10).

One explanation is that a biological mechanism contributes to sex differences. For example, reproductive hormones have been associated with the risk of PD, as there are suggestions of a neuroprotection from estrogen, resulting in a higher susceptibility in men (see Bourque et al. 2009).

Furthermore, women consumed considerably less alcohol than men, which may explain the gender difference if alcohol is an important confounding factor. For example, both low consumption of alcohol and high consumption of milk contributes to low plasma urate levels (see Schlesinger and Schlesinger 2008; Choi and Curhan 2004), which in turn predicts an elevated risk of PD (see Wirdefeldt et al. 2011). Thus, among men, alcohol consumption could mask the potential positive association between milk consumption and PD risk. Unfortunately, information on alcohol consumption was not available in this study using the FMC data. However, in the FMCF, alcohol intake was inquired after, and analyses in that population showed that most women do not consume alcohol (median intake 0 g/d), whereas men do (median intake 36 g/d). Thus, alcohol consumption could explain the gender difference, at least for milk consumption.

6.2 Lifestyle factors and the risk of PD (Studies II and III)

Leisure-time physical activity

In this study, subjects with heavy leisure-time physical activity had a lower risk of PD than those with no activity. This finding is in line with a meta-analysis pooling results from five other prospective studies, which reported an inverse association between physical activity and PD risk (Yang et al. 2015; Thacker et al. 2008). However, two of the studies included in the meta-analysis found the inverse association in men, not women (Yang et al. 2015; Chen et al. 2005), whereas one found it in women, not men (Thacker et al. 2008). Furthermore, one found it in both genders (Xu Q et al. 2010), while one, which included only men, found no association (Logroscino et al. 2006). Our study only found the association in women, not men.

We found that the exclusion of potential underlying PD (i.e. excluding of first 10 years of follow-up time) attenuated the association to non-significant. Thus, the inverse association could be attributed to a decline in leisure-time physical activities among undiagnosed PD patients who are already suffering from preclinical symptoms. Therefore, the effect -modification by sex and BMI on the association between leisure-time physical activity and PD risk found in this study could be interpreted as indicating that women and overweight subjects were more likely to reduce their leisure-time physical activities during the preclinical disease phase. However, it should be noted that the reason for non-significant findings in analyses excluding the first 10 years of follow-up could be due to the small number of subjects engaging in heavy leisure-time physical activity (n=2). After all, the point estimate did not notably change after the exclusion, only the confidence intervals got wider.

Finally, it should be noted that the short-term repeatability of the questionnaire on leisure-time physical activity was rather low. Furthermore, the overall physical activity of the participants could not be examined due to the lack of information on occupational physical activity. This is a limitation, as it could be speculated that those individuals engaged in heavy occupational physical activity might exercise less during their leisure-time.

The possible molecular mechanisms underlying the inverse association between physical activity and PD risk are poorly known. However, as discussed by Thacker et al. (2008), there are suggestions that exercise can induce an increase in neurotrophic factors (Cohen et al. 2003) or in plasma urate concentration (Anderson and Harris 2003; Green and Fraser 1988). Although uric acid levels have been inversely associated with PD risk in several prospective cohort studies (see Wirdefeldt et al. 2011), the mechanism is unknown, but possibly relates to the antioxidant capacity of uric acid. Neurotrophic factors, instead, may confer neuroprotection. An animal model found that forced exercise before injuring the dopaminergic neurons of rats resulted in an increase of glial cell-line derived neurotrophic factor protein, and attenuated the symptoms caused by the injury (Cohen et al. 2003). Also, an animal model of PD showed that physical activity resulted in the attenuation of dopamine depletion in the striatum of rats training on a treadmill, when compared to control animals (Poulton and Muir 2005), which, hypothetically, could attenuate symptoms and slow neurodegeneration.

Smoking

In the current study, an inverse association between smoking and the risk of PD was found, which is in line with the relatively consistent findings of previous studies (see Ritz et al. 2007; see Hernan et al. 2002). There are suggestions that this association is due to reduced sensation-seeking traits of PD patients (Evans et al. 2006). However, the results from this study indicated that the association persisted even after excluding the cases occurring during the first 10 years of follow-up. This challenges the hypothesis that reverse causation, for example a premorbid parkinsonian personality, would account for it.

In contrast to some previous studies (Chen et al. 2010; see Hernan et al. 2002), past smokers did not have a lower risk of PD than those who had never smoked in this study. This lack of association, however, is in line with a recent finding that especially long-term smoking is associated with this reduction of PD risk (Chen et al. 2010). On the other hand, the lack of association between past smokers and PD could be interpreted as supporting the suggestion that smoking cessation could be an early preclinical condition occurring in PD (Ritz et al. 2014).

Unfortunately, the association of duration or amount of smoking could not be examined in the present study, as the number of smoking PD cases was too small. For the same reason, potential effect modification could not be examined in different subgroups. However, a meta-analysis did not find effect modification by sex or education (see Ritz et al. 2007). In this study population, only a minority of smokers were women.

There are plausible, but still debated, hypotheses of biological mechanisms for the potential preventative effects of smoking against PD occurrence, including the neuroprotective effects of nicotine, as reviewed by Quik et al. (2008). Nicotine may act by stimulating nicotinic acetylcholine receptors, which activates various intracellular transduction pathways, including calcium signaling. As a response, adaptations in immune responsiveness and trophic factors may occur, mediating the neuroprotection against neuronal injury (see Quik et al. 2012).

This prospective study appears to lend some support to such hypotheses of a causal association. On the other hand, if smoking is neuroprotective, we would expect it to interact with genetic risk factors of PD, but a recent study documented no interactions between genes and smoking in PD (Chung et al. 2013).

Alcohol consumption

The present study demonstrated that subjects with light to moderate alcohol consumption (alcohol intake >0 but <5 g/d) had an elevated risk of PD, compared to non-drinkers, and that this association apparently was not due to preclinical PD. Heavy consumption of alcohol was not associated with PD risk.

In contrast, most previous studies have showed a significant or non-significant inverse association between alcohol consumption and PD risk, as concluded by two separate reviews (see Bettiol et al. 2015; see Wirdefeldt et al. 2011). We are not aware of any hypothesis for the association found in the present study other than possible confounding related to abstaining from alcohol. Accordingly, when the analyses were restricted to alcohol consumers, a suggestive inverse association between alcohol consumption and PD risk was then revealed.

Residual confounding, possibly due to smoking or coffee consumption, may be an explanation for the inverse association. The good quality of the data in this study, however, does not lend support for this suggestion, as smoking behavior and coffee consumption were reliably measured (Sääksjärvi et al. 2010; Heliövaara et al. 1993).

The exclusion of potential underlying PD did not change the result, at least not in the time span of 10 years. Thus, our study provided evidence against the hypothesis that the reduced sensation-seeking traits of preclinical PD patients would account for the inverse association between addiction-related habits and PD risk (Evans et al. 2006). The attenuation of association to non-significant in the analyses excluding the first 15 years of follow-up could be a result of the small number of subjects.

Unfortunately, subgroup analyses of potential effect-modifying factors could not be examined in this study due to the small number of PD cases. However, it should be noted that most of the alcohol consumers were men in this study population. Only one quarter of women in the study population consumed alcohol, which is consistent with women living in rural areas at the time of baseline (the 1960s and 70s). However, it cannot be ruled out that an underreporting of alcohol consumption may have affected results. In general, the underreporting of alcohol consumption varies by different demographic or consumption-based subgroups of the population, and might be more marked for young men and middle-aged women (Livingston and Callinan 2015).

The possible biological mechanism for the inverse association remains to be clarified. There are suggestions for a contrary hypothesis on positive association between alcohol consumption and PD risk, as alcohol may contribute to oxidative stress through production of alkaloids (see Collins 2002).

Coffee consumption

An inverse association between coffee consumption and the risk of PD was found in the present study. This finding is in line with results obtained from previous cohort studies (Ascherio et al. 2004; Ascherio et al. 2003; Ascherio et al. 2001; Ross et al. 2000).

The inverse association between coffee consumption and PD risk attenuated after exclusion of the potential preclinical disease phase. However, the risk of PD was still reduced by 41% when subjects drinking at least four cups of coffee per day were compared to subjects drinking 0–3 cups per day, after excluding the first 10 years of follow-up. This result argues against the suggestion that a premorbid parkinsonian personality would account for the inverse association by resulting in reduced coffee consumption in future PD cases. To our knowledge, this is a first study to examine the effect of excluding such a long time to account for a preclinical disease phase. Previous studies have not made any exclusions

(Kyrozis et al. 2013; Liu et al. 2012; Ascherio et al. 2004; Ascherio et al. 2003; Ascherio et al. 2001; Ross et al. 2000), or have excluded only the first 2 (Palacios et al. 2012b) or 5 (Hu et al. 2007a) years of follow-up.

In contrast to some previous studies (Ascherio et al. 2004; Ascherio et al. 2001), we did not find any difference in the results between men and women. However, the sex difference found in previous studies could be explained by an interaction with estrogen, as further analyses of those studies showed that the inverse association between coffee and PD risk was present only among women who did not use postmenopausal hormones (Ascherio et al. 2004; Ascherio et al. 2003). At the study baseline, during the 1970s, the number of postmenopausal hormone users was very small (1.9%) and, accordingly, exclusion of the postmenopausal hormone users from the data did not alter the results (data not shown).

Furthermore, the inverse association between coffee consumption and PD was present among subjects who were younger (aged 50–69 years), did no leisure-time physical activity, were overweight, and had a serum cholesterol concentration below the median (<7.24 mmol/l). The median value for serum cholesterol concentration at baseline would be considered high compared to current guidelines, however, those levels reflect the serum cholesterol concentration of the normal Finnish population in the 1970s (Reunanen et al. 1983).

The explanation for the effect modification of these factors remains unclear, but the incidence of PD does increase with age (see Wirdefeldt et al. 2011). Thus, it could be argued that the inverse association between coffee drinking and PD risk was present in the younger age group because younger subjects are not yet affected by the disease progression and may still benefit from drinking coffee. Furthermore, increased physical activity has been associated with lower PD risk (see Wirdefeldt et al. 2011). Obesity might also be involved in the etiology of PD (Chen et al. 2004; Abbott et al. 2002), as found in Studies II and IV, although no interaction between BMI and coffee consumption has been found previously (Ascherio et al. 2004). Finally, another Finnish cohort study found that high total cholesterol is associated with an increased risk of PD (Hu et al. 2008), although the present study (Study IV) did not.

Findings in the present study support the suggested hypotheses of physiological mechanisms for the beneficial effects of coffee consumption against PD. One of the hypotheses rests on the fact that coffee contains a considerable number of potential antioxidants (Yen et al. 2005) and is capable of increasing plasma antioxidant capacity in humans (Natella et al. 2002). Since oxidative stress is suggested as one of the mechanisms underlying PD pathogenesis (see Cardoso et al. 2005), coffee could have neuroprotective effects because of its antioxidant properties. Another hypothesis for the physiological mechanisms of coffee is the role of caffeine as an adenosine A_{2A} receptor antagonist. As suggested by a review, caffeine may protect dopaminergic neurons from excitotoxic components by inactivating A_{2A} receptors (see Schwarzschild et al. 2002).

6.3 Obesity, metabolic health, and the risk of PD (Studies II and IV)

Obesity

Our study consistently revealed a positive association between BMI and PD risk after excluding the first 15 years of follow-up in Study II, and the first 10 years in Study IV. However, previous studies on obesity and the risk of PD have been inconsistent. Two prospective studies found an increased PD risk for subjects with a high BMI (Hu et al. 2006) or an increased triceps skinfold thickness (Abbott et al. 2002), but three other cohort studies found no association (Palacios et al. 2011; Logroscino et al. 2007; Chen et al. 2004). Furthermore, in contrast with our findings, one nested case-control study found an inverse association (Ma et al. 2006).

The inconsistent findings could be due to the preclinical disease phase in PD, as the slow progression of the disease can take decades (see Gaig and Tolosa 2009). Our findings on the effect of excluding the potential preclinical disease phase bring important new aspects into the epidemiological study of PD and obesity. It seems that PD patients start to lose weight several years before the clinical diagnosis (Chen et al. 2003b), so the weight loss is a consequence of the disease process, implying that the preclinical disease stage of PD can mask the real positive association between BMI and the occurrence of PD. Most of the previous cohort studies have excluded the first 3–5 years of follow-up (Palacios et al. 2011; Logroscino et al. 2007; Chen et al. 2004) to rule out the effects of underlying PD, which could explain their lack of association. However, it remains unclear why the other Finnish cohort study (Hu et al. 2006) found the positive association without any exclusion of follow-up time.

The potential biological mechanism remains to be determined, but a clinical observation showed that extremely obese persons had a lower availability of dopamine D2 receptors in the striatum than non-obese controls (Wang et al. 2001). This could predispose them to a higher PD risk. Furthermore, it has also been suggested that lower dopamine receptor availability may lead to compensatory increases in dopamine turnover, consequently increasing oxidative stress and neuronal death (Abbott et al. 2002). In addition, the low-grade chronic and systemic inflammation associated with obesity (see Bastard et al. 2006) could increase the PD risk. Alternatively, the use of pesticides, among other environmental risk factors, has been linked to an increased PD risk (Weisskopf et al. 2010), and adipose tissue might be capable of storing and releasing lipid-soluble environmental neural toxicants.

Metabolic syndrome and factors related to metabolic health

A decreased PD risk for subjects with metabolic syndrome was observed. There are no previous prospective studies predicting PD incidence by the criteria of metabolic syndrome. However, one case-control study reported a lack of association between metabolic syndrome and PD (Cereda et al. 2012). In contrast to our findings, a history of diabetes has been suggested as a risk factor for PD (Hu et al. 2007b), but the evidence from cohort studies is conflicting (see Wirdefeldt et al. 2011; see Cereda et al. 2011).

Further analyses indicated that the inverse association between metabolic syndrome and PD incidence found in the present study was mainly due to the serum triglyceride concentration. There are no previous cohort studies on blood triglyceride or glucose concentrations and PD risk. Our finding is, however, consistent with results from one longitudinal nested case-control study (Vikdahl et al. 2015) and a few case-control studies (Cereda et al. 2012; Scigliano et al. 2006), reporting that high blood triglyceride concentrations were significantly less common in PD cases than controls. However, in contrast to the study by Vikdahl et al. (2014), our study showed that elevated serum triglyceride concentration predicted lower PD risk, even after adjusting for smoking. Furthermore, we also found that hyperglycemia carried a reduced PD risk, consistent with findings from two case-control studies (Cereda et al. 2012; Scigliano et al. 2006).

One explanation for our results regarding metabolic syndrome, triglycerides, and glucose could be the effect of preclinical disease stage of PD. There are observations that PD patients suffer from autonomic disturbances, compromised hypothalamic-pituitary-adrenal axis (Awerbuch and Sandyk 1994), as well as from reduced sympathetic activity (see Wakabayashi and Takahashi 1997). These pathological changes result in, among other things, decreased cortisol and catecholamine concentrations, and lead to lower blood triglyceride and glucose concentrations. Indeed, a study among PD patients found a reduced prevalence of cardiovascular disease risk factors (i.e. diabetes, hypertension, high values of serum glucose,

cholesterol, triglycerides, and total lipids), presumably as a result of the reduced sympathetic activity caused by neurodegeneration (Scigliano et al. 2006).

If the preclinical disease is indeed the underlying reason for our results, they indicate that serum triglyceride concentration could more easily be affected by the reduced sympathetic activity in PD than other metabolic factors. The same applies to the result on glucose concentration, although the association was slightly attenuated after excluding the potential preclinical disease phase. Speculatively, our results are worth noting when planning potential tools for early detection of preclinical PD cases. If reduced triglyceride or glucose concentration is an early sign of mild damage to the autonomic system, the triglyceride or glucose findings from blood tests could be one component in the potential risk score or pre-screening evaluation.

Our prospective study design, however, with a long follow-up period, raises questions about whether the reason for the inverse association is solely the preclinical disease phase. Moreover, our finding suggests that low serum triglyceride concentration could be an independent predictor of PD incidence, as the inverse association between serum triglyceride concentration and PD incidence remained even after the analyses excluding the first 10 years of follow-up.

If serum triglyceride concentration, or fasting plasma glucose concentration, are involved in the etiology of PD, they should have an independent effect. Our results support this suggestion, as a dose-response relationship was found between them and PD risk, after adjusting for potential confounding factors. This is further supported by the fact that adjustments for other components of the metabolic syndrome did not change results (i.e. the results regarding serum triglyceride were adjusted for BMI, blood pressure, serum HDL cholesterol, and fasting plasma glucose; regarding fasting plasma glucose, the adjustment variables were BMI, blood pressure, serum HDL cholesterol, and serum triglyceride).

The inverse association between PD risk and both triglycerides and glucose could be linked to other dopamine-mediated behaviors with reward sensations (e.g. smoking and alcohol consumption) that predict a lower PD risk, as an animal study showed an association between sugar consumption and dopamine release (Rada et al. 2005). High consumption of carbohydrates, especially sugars, is known to increase fasting serum triglycerides (see Chong et al. 2007). On the other hand, this phenomenon might be linked to the association between uric acid and PD, as uric acid is a by-product of uncontrolled fructose metabolism (see Chaudhary et al. 2013). Apart from these speculations, we have no suggestions for potential mechanisms behind the associations between elevated triglycerides, hyperglycemia, and reduced PD risk. Serum triglyceride concentration, or fasting plasma glucose concentration, could also be a marker for some other unknown confounding factor.

It is not clear, however, whether 10 years is long enough to exclude the effect of the preclinical disease phase. When and where the neuropathological process develops in PD remains uncertain, but a recent review suggested that the non-motor symptoms of PD could begin decades before the onset of motor symptoms, although the start and progression of premotor PD is highly variable (see Gaig and Tolosa 2009). Thus, the potential effect of a preclinical disease phase on the components of metabolic syndrome cannot be ruled out.

The present study found no association between blood pressure and risk of PD. This lack of association is in line with some previous prospective findings (Simon et al. 2007). However, the evidence is conflicting, as reduced (Vikdahl et al. 2015; Paganini-Hill 2001) or increased (Qiu et al. 2011) PD risks have been found for subjects with hypertension. One reason for this discrepancy could be the differences in exposure information – some studies actually measured the blood pressure of participants (Vikdahl et al. 2015; Qiu

et al. 2011), while others relied on information of hypertension diagnosis that was self-reported or gathered from medical records (Simon et al. 2007; Paganini-Hill 2001).

Furthermore, this study found no association between serum HDL cholesterol and PD risk, which is in line with previous prospective studies (Huang et al. 2008; de Lau et al. 2006b). However, at the time of baseline examinations, the population had rather high HDL cholesterol values. Thus, the lack of association in this study could be due to the small number of PD cases with reduced serum HDL cholesterol concentrations. In other words, the population was not heterogeneous enough to examine the association between HDL cholesterol concentration and PD risk (less than 15% of the subjects had HDL cholesterol concentrations under the cut-off point of 1.3 mmol/L, and 80% of the subjects, from the first decile to the ninth decile, had HDL values between 1.22 and 2.22 mmol/L).

Serum total cholesterol concentration also did not predict the incidence of PD in this study. Previous findings have been inconsistent, reporting reduced (Simon et al. 2007; de Lau et al. 2006b) or increased (Hu et al. 2008) PD risk for increasing total cholesterol levels. Though the reasons for this inconsistency are unclear, it could, in general, be due to many factors such as methodological differences or problems (e.g., population demographics, exposure information, difficulties in case ascertainment, residual confounding).

Finally, the definition of metabolic syndrome and the cut-off values for categories of the components of metabolic syndrome were based on the harmonized definition of metabolic syndrome (Alberti et al. 2009). Unfortunately, we did not have information on waist circumference in our data; thus, BMI was used as a proxy measure in the definition of metabolic syndrome by replacing the waist circumference category 'normal' with a BMI <25 kg/m^2 and the category 'large' with a BMI ≥25 kg/m^2. As described in chapter 4.2.1, there was high correlation between waist circumference and BMI in the Health 2000 data.

However, the use of a proxy measure could cause confounding in Study IV, as one reason for elevated triglyceride concentration is a large waist circumference associated with a fatty liver. However, there are findings that BMI also independently predicts fatty liver (Kotronen et al. 2013). Furthermore, the association between triglycerides and PD incidence did not change, even after adjusting for BMI and other causes of elevated triglycerides (i.e. alcohol consumption and impaired glucose metabolism marked as having a high fasting plasma glucose concentration).

6.4 Methodological considerations

6.4.1 Strengths and limitations

The main strengths of the present study are its prospective design, a comprehensive set of baseline measurements, and a long follow-up period.

The participation rate in all three surveys was high (82.5% in the FMC, 78.6% in the FMCF, and 90.2% in the Mini-Finland Health Survey). Thus, the general concern that those who do not participate have different health attributes than those participating in the survey has little effect in this study. Furthermore, the Mini-Finland Health Survey was a representative sample of the Finnish population of adults aged 30 years and over, and thus the results from Study IV could be generalized to the whole adult population. However, the FMC and its follow-up survey were not completely representative of the Finnish population (Aromaa 1981). This, however, is not a concern due to the etiological nature of the present study, and the exclusion of the eldest age groups from the analysis.

Causality cannot be evaluated from observational studies alone. Nevertheless, the prospective study design is a major advantage in studies attempting to find new etiologic clues. In comparison, a cross-sectional or case-control study design cannot evaluate whether the exposure has occurred before the event, which is one of the criteria for causation. However, the long preclinical disease phase of PD (see Gaig and Tolosa 2009) raises concerns that, despite the prospective design, it cannot be concluded with certainty that the exposure was measured before the outcome occurs. Thus, we attempted to address this concern with sensitivity analyses, i.e. excluding the first 10–15 years of follow-up time. This, however, led to rather small numbers of PD cases, so these results must be interpreted with caution. Nevertheless, these sensitivity analyses gave valuable new insights into the interpretation of the results. Overlooking these kinds of sensitivity analyses in previous studies could explain the inconsistent results in the literature regarding PD epidemiology.

Repeatability of the exposure factors were studied (as described in chapter 4.2.3), and was found to be relatively high. Thus, the associations observed were unlikely weakened by inaccurate measurements. There were, however, a few exposure factors with rather low repeatability, such as the consumption of berries and leisure-time physical activity, which raises concerns. The seasonal availability of berries may have affected the agreement between measurements taken several months apart. Additionally, there is this notion that foods consumed close to the assessment of a person's habitual past diet intake may influence responses, possibly creating a bias toward recently consumed food (Fowke et al. 2004). The seasonal variability in physical activity habits may have also affected the repeatability. However, despite the low repeatability, the methods have probably been able to capture the exposure with enough precision to have allowed for ranking individuals in the correct order. Thus, we were able to find the associations between these exposure factors and PD risk.

A long follow-up time is a major advantage in an epidemiological study of a disease that has a long preclinical phase and progresses slowly. The long preclinical disease phase of PD has not received much attention in previous studies, but the present study highlights the effect of taking it into account and demonstrates the need for a very long follow-up time. This especially affects the associations between metabolic syndrome, obesity, and PD, as discussed above. The disadvantage of a long follow-up period is, however, that the prediction of single-exposure measurements weakens over time. For this reason, we did not expand the follow-up periods any further, and a shorter follow-up time was even applied in some analyses.

It is possible that long-term changes in people's behaviors, decades after the baseline health examinations, may have caused conservative estimates of the associations. For example, there are observations that coffee consumption has decreased in Finland over the last two decades (Helakorpi et al. 2004), which could have attenuated the estimated relative risks in this study. During the follow-up of this study, changes in smoking and alcohol consumption also occurred. The proportion of abstainers has decreased, and alcohol consumption increased between the 1980s and 2004, especially among women (Helakorpi et al. 2004). Smoking decreased in men and increased in women during the 1980s, but has remained at the same level since the mid-1990s in men and late 1980s in women (Helakorpi et al. 2004). Discussion on long-term population changes in diet continues in the next chapter (6.4.2). Furthermore, sociodemographic factors, such as marital status, education, and occupation, are likely to change over a long follow-up period, which may have resulted in residual confounding.

The study populations used, the FMC, the FMCF, and the Mini-Finland Health Survey, are well-characterized cohorts with a comprehensive set of baseline measurements. The good quality of the data in this study (see chapter 4.2.3) and the ability to adjust for major confounding factors reduces the

concern of residual confounding. However, residual confounding may still remain due to factors influencing PD that were unknown or not available in the data. For example, the presence of an unknown confounding factor might be one reason for the rather wide confidence intervals in Study I regarding the individual food groups and items. Potential confounders include factors presented in Figure 1, and, for example, serum urate concentration is a factor lacking from this study. However, the FMCF does include a sub-population with information on serum urate concentration, though preliminary analyses showed that serum urate concentration was not associated with PD risk (Paul Knekt, personal communication, 2015).

Regarding Study I, certain lifestyle factors that are commonly considered to increase the risk of CVD seem to be inversely associated with the risk of PD in the present study, for example, consumption of foods that are major sources of saturated fat (processed meat and sausages), smoking, and the consumption of unfiltered boiled coffee (see Erhardt 2009; see van Dam 2008; see Srinath Reddy and Katan 2004). Furthermore, the consumption of foods containing antioxidant vitamins (fruits and berries) was associated with an increased risk of PD in men, even though they were associated with a lower risk of CVD in this same FMC data (Knekt et al. 1994). The explanation for these rather opposing results on PD and CVD could be that these two diseases do not share similar pathogenic processes. Another explanation could be that population selection occurred due to deaths caused by CVD before an individual even had a chance to reach the typical age of PD onset, and this may cause bias if these diseases have shared risk factors.

Finally, it cannot be excluded that the small number of PD cases or multiple comparisons may have caused chance findings. This is of particular concern in Study I, with its somewhat unexpected results. Furthermore, the relatively small number of PD cases did not allow for all of the planned interaction analyses to be performed. In addition, these were exploratory results of uncertain interpretation, and future studies on this topic are needed.

6.4.2 Methodological considerations related to the dietary method

Dietary history interview

In the FMC, the method for measuring the total habitual food consumption of the participants was a one-year dietary history interview. The dietary history interview is considered to be the best method for measuring an individual's habitual dietary intake in the long term (see Virtanen and Pietinen 1999). However, the interview is subject to the participant's own assessment, and a 12-month time period might be a lengthy time to recall. To minimize potential biases related to the method, food models were used to diminish errors in recall, open-ended questions allowed for more specific answers, and trained interviewers used a structured questionnaire to reduce the differences between the interviewers. However, the method is also reliant on the skills of the interviewer. Thus, the repeatability of the method was examined (Järvinen et al. 1993).

The repeatability of the method was found to be good at short-term (measured twice, at an interval of 4–8 months), but declined at long-term (measured twice, at an interval of 4–7 years) (Järvinen et al. 1993). This implies that the method was accurate, but dietary habits changed over the long term. Indeed, during the period from 1972 to 1992, the diet in Finland was changing; the total fat content decreased from 38% of energy to 34%, saturated fat from 21% to 16%, polyunsaturated fat from 3% to 5%, and the intake of cholesterol decreased by 16% (Pietinen et al. 1996). Furthermore, fruit and vegetable consumption increased two- to three-fold, and a shift from boiled to filtered coffee occurred. It cannot be excluded that the lack of an association is merely due to changes in dietary habits during the extremely long follow-up

period. However, these changes occurred slowly over a 20-year time period, and the subjects in this study had already had a long exposure to their typical diet at the time of baseline examination in 1966–1972.

Food composition values

The present study mainly examined the diet quality and foods groups and items. Information on polyunsaturated, saturated, and trans fats were, however, included in the mAHEI. Originally, the food composition database was compiled utilizing the contemporary Finnish food composition tables (Turpeinen and Roine 1967), and was updated during late eighties based on the nutrient composition book published by the Finnish Social Insurance Institution (Rastas et al. 1989). However, it is difficult to assess the agreement between the analyzed values of food samples collected during the 1980s and the actual food composition at the baseline of this study in 1966. Nutrient composition of foods and food preparation techniques have changed over time. However, ranking according to intakes is commonly used in epidemiologic studies, and thus, the absolute intake levels are not as important as the ability of the method to rank subjects in the correct order.

Furthermore, nutrient contents of the foods referred mainly to raw foodstuffs in the FMC data (Järvinen 1996). Thus, the effect of food preparation and food storage on nutrient content has not been taken into account. However, as the present study mainly evaluated food use and diet quality, this is not a concern.

Dietary index

To replicate the finding by Gao et al. (Gao et al. 2007), we formed the AHEI index in our database using components as similar as possible to the original work. A few modifications were made to adjust the index for the present study population. We believe that the mAHEI in our study was adequately comparable, as both the AHEI and our mAHEI reflected the diet quality by rewarding higher scores for the high intake of fruits, vegetables, legumes, whole grains, nuts, fish, and poultry, and for a low intake of saturated fat and trans fat. However, in comparison with the AHEI, information on multivitamin use and alcohol consumption could not be included, since these variables were not available in the FMC data. However, the use of vitamin supplements was rare at the time, so including them would probably not have affected the result. Furthermore, alcohol consumption among women was presumably very low at the time of study, as was the case in the FMCF 4–7 years later. Thus, the lack of information on alcohol consumption probably did not affect our results for women. Instead, among men, the lack of alcohol consumption in the mAHEI could explain the opposing findings in our study compared to the study by Gao et al. (2007).

In addition, the AHEI contained a variable on fiber intake from grain sources (g/d). However, in our modification this was replaced with intake of whole grain items (g/d, products containing >25% whole grain), because the variable on fiber intake included fiber from all sources in our data. Additionally, it should be noted that berry consumption was not included in the total fruit consumption variable, as was done in the original AHEI.

Furthermore, the scoring system was different in the mAHEI than the original AHEI. We did not set recommended intake levels as the cut-off value for those receiving the highest scores. Instead, we divided the intakes into quintiles and scored them according to the AHEI scoring principles. This was done due to the etiologic nature of our study. We wanted to rank the subjects by their healthy eating habits, and were less interested in whether the intake values were above or under the recommended intake level. Furthermore, our scoring system was also reasonable due to the dietary method being based on food

frequencies, as the method does not measure absolute intake levels of foods or nutrients, it rather ranks subjects in the correct order by their intake levels.

On the other hand, we should have considered how well the mAHEI reflected the diet quality of the Finnish population during the 1960s. Instead of replicating the study by Gao et al. (2007) in detail, maybe even more attention should have been given to adapting the dietary index to the Finnish diet common at the time. For example, the variable on trans-fat intake could have received less weight in the total score of the index, as intake of trans fat was very low. However, these are rather minor concerns, as it seems that the mAHEI is a good tool for assessing diet quality since it had a strong inverse association with CVD mortality in the present study population (Sääksjärvi et al. 2015).

6.4.3 Case ascertainment

Diagnostic accuracy is a challenge in epidemiologic studies of PD. The most reliable antemortem diagnostic method is expert neurologic examination (see Tanner and Goldman 1996).

In this study, the linkage with the Drug Reimbursement Register of the SII assured that subjects with PD were identified from the cohort by means that included clinical neurologic examination, a certificate describing the clinical diagnostic criteria, and an inspection of this certificate by two independent medical experts at the SII.

It is possible that the study population includes undiagnosed PD cases, although this would not be expected to have great importance, since false-negative cases have no considerable effect on estimated relative risks, as the prevalence of PD is low in the normal population [approximately 1% among subjects over age 65 (see Hirtz et al. 2007)]. Furthermore, due to the free medication coverage, it could be expected that the majority of PD patients will apply for the allowance and thus be included in the Drug Reimbursement Register of the SII.

Moreover, the possibility that all patients with PD diagnoses were not true PD cases may have biased the estimates of the strength of association, but this risk was shown to be minor, as our study neurologist (Dr. Jukka Lyytinen) retrospectively compared a sample of the certificates for PD medication reimbursement against hospital records and found the agreement to be 80%.

Additionally, it should be noted that the criteria for eligibility for the reimbursement right code 110 may have changed over time. Currently, the reimbursement right code 110 includes certain other movement disorders that may either resemble PD (e.g. vascular parkinsonism) and/or benefit, at least partially, from dopaminergic therapy. These also include atypical parkinsonian disorders, such as progressive supranuclear gaze palsy and multiple system atrophy (corresponding to ICD-10 codes G23 and G90.3, respectively), as well as the heterogeneous group of dystonic disorders (ICD-10 codes G24.1 and G24.8). It was not until the end of the 1990s that the information on these specific diagnostic codes as a basis for the reimbursement right code 110 were incorporated into the register. This is a limitation to our study, as we cannot differentiate these diagnoses to be able to identify solely the cases with idiopathic PD. However, the number of diseases other than idiopathic PD (e.g. patients with a primary dystonic disorder) among the subjects with the reimbursement right code 110 is presumably very small. Primary dystonia (focal or generalized) is an extremely heterogeneous group of disorders, that – despite some benefit from dopaminergic therapy – generally is clinically quite distinct from parkinsonism. Atypical parkinsonian disorders, such as progressive supranuclear palsy and multiple system atrophy, are much rarer than PD, with an estimated prevalence ranging from 1 to 6 per 100,000 (Schrag et al. 2000; Schrag et al. 1999). Among the Health 2000 participants, where the reimbursement right code 110 can be differentiated by

the diagnosis codes (for those entered into the SII's register after the end of the 1990s), none of the subjects with reimbursement right code 110 had disease codes other than idiopathic PD (Harri Rissanen, personal communication, 2015). Furthermore, as stated above, the evaluation of a sample of the certificates for the reimbursement right code 110 supported this suggestion (see chapter 4.3.3 for details).

The crude annual PD incidence in our study populations (31.9-44.7/100,000 in Studies I-IV) was roughly 2-2.5 times higher than the crude annual incidence in 1992 (17.2/100,000) from a study conducted in southwestern Finland (Kuopio et al. 1999). The difference could arise from several reasons, such as a different time period, geographical area, or age distribution, as well as the above mentioned imprecision in PD diagnosis.

Furthermore, the method for case ascertainment includes some delay between symptom onset and the date of entering the Drug Reimbursement Register of the SII. This was, however, taken into account while excluding the first 10 or 15 years of follow-up. This exclusion was also supported by a recent review suggesting that the non-motor symptoms of PD could start decades before the onset of motor symptoms (see Gaig and Tolosa 2009).

Finally, the practices of the clinical diagnosis of PD have changed since the beginning of the FMC in 1966. Based on information from the Drug Reimbursement Register, the prevalence of PD was increasing during the 1970s (see Figure 5), probably due to improved diagnostic accuracy, but also due to improved therapy with an impact on the long-term prognosis of PD. After that time period, the prevalence stayed at the same level during the rest of the follow-up time in this study. It cannot be excluded that this affected the results of the studies from the FMC (baseline in 1966–1972) and the FMCF (baseline in 1973–1976). If the data included unidentified PD cases, missed during the 1970s, it may have attenuated the estimates of the strength of association, or even resulted in a lack of association. However, due to the low prevalence of PD, this is unlikely. Furthermore, the changes occurred only during the first decade of the 41-year follow-up of the FMC and during the first few years of the 22-year follow-up of the FMCF. It is more plausible that the association would be emphasized during the long follow-up and thus the uncertain case ascertainment at the beginning of the follow-up is inconsequential. Furthermore, this does not concern the Mini-Finland Health Survey conducted in 1978–1980, as the baseline was at the same time as the prevalence stabilized.

If the diagnosis of PD was uncertain or underdiagnosed during the 1970s, it may be that the sensitivity analyses we performed to exclude the potential preclinical disease phase did not capture solely the effect of potential underlying PD. Instead, these analyses may have also served as a clearing period: after excluding the first 10 years of follow-up, the analyses included more reliable PD cases. This would explain why the positive association between BMI and PD risk was revealed after exclusion of the first 15 years in the FMCF, but in the Mini-Finland Health Survey exclusion of 10 years was sufficient.

6.5 Implications for future epidemiologic research

The findings of this study should be replicated in other populations, especially regarding the results from Study IV, which was among the first of prospective studies examining the associations between blood triglycerides, glucose, and PD risk. Similarly, the findings on diet quality and PD risk should be replicated, as there is only one previous prospective study in addition to Study I on this topic. More prospective studies on the association between nutrients and PD risk are also needed.

Overall, the number of prospective studies on PD and different exposures is rather limited. Other population-based cohorts, nationally and internationally, should make efforts to expand the study of

chronic diseases to include PD epidemiology, as surely there are eligible cohorts that have not attempted to identify PD cases yet. Recently, the EPIC-cohort, which includes several countries, went through a screening procedure to identify PD cases (Gallo et al. 2015), and results for further analyses on PD epidemiology are expected soon.

Many of the initial studies on the epidemiology of PD were too small or methodologically limited, which should be considered when planning new studies. However, the low prevalence of PD in the general population is a challenge for increasing the size of studies. Furthermore, the multifactorial etiology of PD, where multiple environmental factors influence genetically predisposed individuals who are aging, makes observational studies on PD challenging. de Lau and Breteler (2006a) suggest that better insight into the role of environmental factors in the pathogenesis of the disease will be gained through the pooling of studies to further increase statistical power. This would also allow a more comprehensive examination of potential effect-modifying factors. However, different case ascertainment methods across studies may complicate creating uniform pooling procedures.

Temporal aspects should be studied as an effect-modifying factor on the association between different exposures and PD risk as well. It is possible that there is a certain time window for the potential risk or protective factors to influence the risk of PD. For example, it would be of importance to study whether the associations between exposures and PD risk appear or disappear depending on the age of the subjects at baseline (early adulthood vs. middle age vs. old age), or at the time of PD diagnosis (representing the early onset vs. late onset phenomenon of the disease).

Furthermore, the findings of this thesis covered a set of dietary and other lifestyle factors, as well as metabolic factors, but the data used in this study offer many more important areas to continue epidemiological studies of PD, such as the associations between PD risk and medication use, or previous illnesses.

7 Summary and conclusions

Lifestyle factors, as well as metabolic health, may predict the incidence of PD. The main conclusions of this study could be stated as follows:

- Most of the individual food groups or items considered, as well as the diet quality, did not predict the incidence of PD. However, a high consumption of milk was associated with an increased PD risk in women. In addition, an inverse association was observed for the consumption of berries, as well as processed meat and sausages, among women. Among men, an increased risk of PD was observed for a high consumption of fruits and berries, and for consumption of fresh fruits. However, the possibility of a chance finding due to multiple comparisons is a concern. The exclusion of the potential preclinical disease phase did not change the results for women, but for men, the associations disappeared.
- Subjects with heavy leisure-time physical activity had a 73% lower risk of PD than those with no activity. Our results, with the prospective study design, support the hypothesis that physical activity is beneficial for neuroprotection. However, reverse causation cannot be ruled out, as this inverse association might be attributed to a decline in leisure-time physical activities among undiagnosed PD patients already suffering from preclinical symptoms decades before PD onset.
- Current smokers had a 77% lower risk of PD than those who had never smoked. The association persisted even after the exclusion of the first 10 years of follow-up, thus challenging the hypothesis of reverse causation.
- In subjects with light to moderate alcohol consumption (alcohol <5 g/d) the risk of PD was elevated by 81%, compared to non-drinkers. Heavy consumption of alcohol, however, was not associated with PD risk.
- Subjects who consumed at least 10 cups of coffee per day had a 76% lower PD risk, compared to non-drinkers. The association attenuated little after excluding the presumable preclinical disease phase, but subjects drinking at least four cups of coffee per day still had a 41% lower PD risk than those drinking three cups or less.
- This study revealed a positive association between BMI and PD risk, after exclusion of the potential preclinical PD phase (i.e exclusion of the first 10 to 15 years of follow-up).
- A reduced PD risk for subjects with metabolic syndrome was observed. It appears this association was mainly due to serum triglyceride and fasting plasma glucose concentrations. Elevated triglyceride and glucose concentrations predicted lower PD risk even after exclusion of the first 10 years of follow-up. However, it remains unclear whether this exclusion is long enough to take into account the entire preclinical disease phase. Thus, the result may be interpreted as an early marker of the neurodegenerative process.
- No association between serum HDL cholesterol, or serum total cholesterol concentration, or blood pressure and PD risk was observed.

Our findings on the effect of excluding the potential preclinical disease phase brought important new aspects into the epidemiological study of PD, highlighting the importance of acknowledging the potential preclinical disease phase that can even be decades in PD. However, caution is needed when interpreting these results, as the number of PD cases was rather small after the exclusion. Furthermore, due to the long preclinical disease phase of PD, reverse causation cannot be excluded, despite the prospective study design.

In light of the present study and previous findings, there are very few dietary factors predicting the risk of PD. However, the number of studies is so small that more studies are needed before making conclusions about the associations between diet and PD risk.

Regarding lifestyle factors, this study agreed with previous findings suggesting that smoking, or coffee drinking, has an inverse association with PD risk. Due to the hypothesis that nicotine might have neuroprotective properties, there is currently one ongoing phase II randomized controlled trial investigating the effects of transdermal nicotine patches on PD patients (see Kalia et al. 2015b). The results from it will indicate whether this hypothesis needs to be revisited. Similarly, caffeine has been hypothesized to be a neuroprotective agent, and a long-term phase III randomized controlled trial investigating caffeine treatment for PD has been initiated (see Kalia et al. 2015b). A pilot study among PD subjects found improvement in motor symptoms for caffeine users, when compared with placebo users (Postuma et al. 2012).

Summarizing the present and previous findings, physical activity seems to be inversely associated with PD risk, whereas the role of alcohol consumption, in relation to PD risk, remains uncertain. There are several randomized controlled trials investigating physical activity in PD patients, and it is clear that endurance exercise training improves physical conditioning in PD patients (see Lamotte et al. 2015). However, it is not clear whether exercise actually modifies disease progression, or if it even affects the motor symptoms of PD.

The epidemiologic evidence for the association between BMI and PD risk is controversial and rather scarce, but adulthood obesity before the first preclinical symptoms of PD could be a risk factor for the disease. Even less evidence is available for evaluating the association between metabolic factors and PD risk, and future studies on this topic are evidently needed.

For clinical use, a risk score assessing an individual's risk of developing PD is needed. If disease-modifying therapy could be developed, it would be beneficial to administer it as early during the disease course as possible, preferably before the development of motor symptoms. The risk score would be helpful in identifying subjects at risk for PD and thus potential subjects for more intensive screening (e.g. imaging techniques currently under development for PD diagnosis). The score would include topics that have been associated with future risk of PD and considered as early markers of the disease, such as olfactory deficit, constipation, and perhaps, as suggested by the present study, low serum triglyceride and fasting plasma glucose concentrations. Finally, questions on physical activity, smoking habits, coffee consumption, and BMI could also be included.

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Appendix tables

Appendix table 1. An example of the literature search strategy, spring 2015. The following terms were used for the search in the PubMed database for all the possible relevant studies.

PD and physical activity				
activit*	AND	cohort	AND	parkinson*
exercise*		prospective		
workout		longitudinal		
training		follow?up		
conditioning		incidence		
exertion		occurrence		
fitness		relative risk		
sport*		hazard*		
		rat*		
		ratio*		
		risk*		
		cox*		
PD and alcohol consumption				
alcohol*	AND	cohort	AND	parkinson*
ethanol*		prospective		
wine*		longitudinal		
beer*		follow?up		
cider*		incidence		
strong*		occurrence		
liqueur*		relative risk		
booze*		hazard*		
spirit*		rat*		
drinking		ratio*		
consum*		risk*		
		cox*		

Appendix table 2. The food grouping and distribution used in the analyses for Study I, presenting also the three additional nutrients included in the mAHEI.

Food groups	Content, unit g/day (sum of all items included)	Tertiles (T1, T2, T3) (or 0 g/d vs. >0 g/d)	
		Men (g/d)	Women (g/d)
Grains	all grains	10-236, 237-342, 343-1535	20-170, 171-249, 250-1092
Rye	rye	0-96, 97-181, 182-1026	0-60, 61-120, 121-951
Wheat	wheat	0-75, 76-149, 150-854	2-63, 64-115, 116-769
Whole grain (defined as products containing >25% wholegrains. Categorization made by Jukka Montonen)	cereal products that contain >25% whole grain, e.g. rye flour, dried rye bread, hard rye bread (crispbread), soft rye bread, potato rye bread, sweet and sour bread, wheat flour (graham), wheat germ, semolina (whole wheat), graham rusk, graham bread, dark wheat bread, bread with mixed flour, millet, rolled oats, barley flour, barley (pearl), buckwheat, barley bread, unleavened barley bread	0-152, 153-240, 241-1321	0-102, 103-166, 167-963
Vegetables	all vegetables	5-272, 273-397, 398-1354	10-220, 221-317, 318-1026
Legumes and nuts	legumes and nuts	0-3, 4-7, 8-101	0-1, 2-5, 6-250
Potato	potato	1-186, 187-289, 290-1072	0-121, 122-192, 193-896
Roots	roots	0-9, 10-30, 31-356	0-16, 17-44, 45-579
Fruits and berries	all fruits and berries, fruit juices (not jams or juices with added sugar)	0-64, 65-146, 147-1094	0-106, 107-203, 204-1325
Fruits, fresh	orange, avocado, banana, grapefruit, cherry, plum, apple, peach, pear, lemon, watermelon, grapes, fruit salad (no canned or dried fruits)	0-19, 20-82, 83-906	0-47, 48-135, 136-1078
Berries	cranberry, gooseberry, strawberry, black currant, blueberry, red currant, lingonberry, cloudberry, sea buckthorn berries, raspberry, fresh berries average (no jams)	0-4, 5-14, 15-308	0-8, 9-18, 19-246
Butter and lard	butter, lard	0-38, 39-60, 61-272	0-25, 26-41, 42-240
Margarines	soft vegetable margarine (Flora, Solive)	0-1, 2-4, 5-211	0-1, 2-4, 5-154
Oils, mayonnaise	fish oil, vegetable oil, mayonnaise	0 g/d vs. >0 g/d (1-68g)	0 g/d vs. >0 g/d (1-80g)
Milk and milk products	all milk and milk products	13-764, 765-1142, 1143-3550	8-540, 541-793, 794-3283
Milk	standard milk (3.9% fat), low-fat milk (2.5% fat), skimmed milk, beestings	0-545, 546-950, 951-3500	7-370, 371-613, 614-3247
Fermented milk products	yogurt , buttermilk, curdled milk, curd	0, 1-150, 153-2000	0-23, 24-166, 167-2000
Cheese	edam cheese (40% fat), edam cheese (20% fat), emmental cheese, blue cheese, homemade goat cheese, homemade cheese, processed cheese, processed cheese (high fat)	0-2, 3-10, 11-182	0-2, 3-10, 11-242

Meat and meat products	all meat and meat products	0-105, 106-181, 182-1257	0-67, 68-115, 116-819
Red meat	medium fat pork, lean pork, ham (pork), chop with bones (pork), pork loin, medium fat beef, beef steak, veal, veal steak, veal brisket, lean mutton, mutton joint	0-56, 57-101, 102-708	0-37, 38-67, 68-784
Processed meat and sausages	bacon, pork back fat, salami-type dry sausage, horse meat, canned pork, canned pork and beef, canned beef, jelly veal, sausages (“Berliini”, “Tee”, “Lauantai”, “Gotler”, ”Suomi”, “Balkan”, “cheap”, frankfurter, fresh pork, and sausage stuffed with pearl barley)	0-27, 28-61, 62-773	0-13, 14-35, 36-379
Poultry	broiler, chicken	0 g/d vs. >0 g/d (1-250g)	0 g/d vs. >0 g/d (1-96g)
Ratio of white:red meat	(chicken + broiler + fish)/(all meat and meat products - (chicken + broiler))	0-0.16, 0.16-0.36, 0.36-80	0-0.16, 0.16-0.36, 0.36-39
Fish	all fish and fish products	0-19, 20-45, 46-817	0-12, 13-27, 28-415
Eggs	eggs	0-17, 18-36, 37-501	0-12, 13-30, 31-242
Sugar and sugar-rich condiments	sugar, jam, marmalade, honey, syrup	0-37, 38-63, 64-317	0-31, 32-55, 56-508
PUFA	polyunsaturated fatty acids	1.3-6.0, 6.1-8.8, 8.9-74.2	0.8-4.3, 4.4-6.4, 6.5-52.8
SAFA	saturated fatty acids	11-56, 57-77, 78-279	8-38, 39-54, 55-179
trans fats	trans fats	0.3-1.8, 1.9-2.6, 2.7-24.8	0.2-1.3, 1.4-2.0, 2.1-18.0