PUBLICATIONS OF
THE UNIVERSITY OF EASTERN FINLAND

Dissertations in Health Sciences

ANNE PAAKINAHO

DISEASE-MODIFYING ANTIRHEUMATIC DRUGS AND INHALED B2-ADRENOCEPTOR AGONISTS AND RISK OF PARKINSON'S DISEASE

A NATIONWIDE REGISTER-BASED STUDY

DISEASE-MODIFYING ANTIRHEUMATIC DRUGS AND INHALED B2-ADRENOCEPTOR AGONISTS AND RISK OF PARKINSON'S DISEASE

A NATIONWIDE REGISTER-BASED STUDY

Anne Paakinaho

DISEASE-MODIFYING ANTIRHEUMATIC DRUGS AND INHALED B2-ADRENOCEPTOR AGONISTS AND RISK OF PARKINSON'S DISEASE

A NATIONWIDE REGISTER-BASED STUDY

To be presented by permission of the Faculty of Health Sciences,
University of Eastern Finland, for public examination in SN201 Auditorium,
Kuopio, on February 9th, 2024, at 12 o'clock noon

Publications of the University of Eastern Finland
Dissertations in Health Sciences
No 803

School of Pharmacy
University of Eastern Finland, Kuopio
2024

PunaMusta Oy
Joensuu, 2024
Distributor: University of Eastern Finland
Kuopio Campus Library

ISBN: 978-952-61-5094-9 (print)
ISBN: 978-952-61-5095-6 (PDF)
ISSNL: 1798-5706
ISSN: 1798-5706
ISSN: 1798-5714 (PDF)

Author's address: Faculty of Health Sciences, School of Pharmacy
University of Eastern Finland
KUOPIO
FINLAND

Doctoral programme: Doctoral Programme in Drug Research

Supervisors: Professor Anna-Maija Tolppanen, PhD
Faculty of Health Sciences, School of Pharmacy
University of Eastern Finland
KUOPIO
FINLAND

Professor Emerita Sirpa Hartikainen, MD, PhD
Faculty of Health Sciences, School of Pharmacy
University of Eastern Finland
KUOPIO
FINLAND

Docent Miia Tiihonen, PhD (Pharm)
Faculty of Health Sciences, School of Pharmacy
University of Eastern Finland
KUOPIO
FINLAND

Docent Marjaana Koponen, PhD (Pharm)
Faculty of Health Sciences, School of Pharmacy
University of Eastern Finland
KUOPIO
FINLAND

Reviewers:

Associate Professor Björn Pasternak, MD, PhD
Clinical Epidemiology Division
Department of Medicine Solna
Karolinska Institutet
STOCKHOLM
SWEDEN

Professor Mika Gissler, PhD
THL Finnish Institute for Health and Welfare
Department of Knowledge Brokers
HELSINKI
FINLAND
University of Turku, Research Centre for Child Psychiatry and Invest Research Flagship
TURKU
FINLAND
Region Stockholm, Academic Primary Health Care Centre
Karolinska Institutet, Department of Molecular Medicine and Surgery
STOCKHOLM
SWEDEN

Opponent:

Professor Olaf H. Klungel, PharmD, PhD
Division of Pharmacoepidemiology & Clinical Pharmacology
Utrecht Institute for Pharmaceutical Sciences
Utrecht University
UTRECHT
THE NETHERLANDS

Paakinaho, Anne
Disease-modifying antirheumatic drugs and inhaled β2-adrenoceptor agonists and risk of Parkinson's disease: a nationwide register-based study
Kuopio: University of Eastern Finland
Publications of the University of Eastern Finland
Dissertations in Health Sciences 803. 2024, 161 p.
ISBN: 978-952-61-5094-9 (print)
ISSNL: 1798-5706
ISSN: 1798-5706
ISBN: 978-952-61-5095-6 (PDF)
ISSN: 1798-5714 (PDF)

ABSTRACT

Despite active research, the aetiology of Parkinson's disease (PD) is not fully understood. Increasing age is the most consistently associated risk factor, but further understanding of modifiable risk factors, such as drugs, is needed. The identification of drugs associated with reduced PD risk could aid in the discovery of new treatments for PD, by elucidating molecular mechanisms that affect PD development. Risk factor studies are challenged by the long prodromal period before symptoms meet PD diagnostic criteria.

This thesis examined whether disease-modifying antirheumatic drugs (DMARDs) used in rheumatoid arthritis (RA) (Study II) and inhaled β2-adrenoceptor (β2AR) agonists used in asthma and chronic obstructive pulmonary disease (COPD) (Study III), are associated with PD risk. RA has been associated with reduced PD risk, which could be related to immunomodulatory effects of DMARDs. This topic is, however, largely unexplored. According to experimental studies, β2AR agonists can reduce the expression of α-synuclein, a key protein in PD pathology, but the epidemiological evidence of the relationship between β2AR agonists and PD remains inconsistent.

Reverse causality refers to a situation wherein drug exposure is influenced by prodromal symptoms of PD. To limit reverse causality, an

appropriate drug exposure assessment period was evaluated by studying the incidence of muscle relaxant use as proxy for the onset of prodromal muscle symptoms (Study I). To limit potential confounding by indication, Studies II and III had an indication-restricted design. Study II was restricted to RA and Study III to asthma/COPD.

This thesis was based on the register-based Finnish Parkinson's disease study (FINPARK) that includes community-dwelling Finnish residents who received a clinically verified PD diagnosis during 1996-2015 and their comparison persons matched for age, sex, and hospital district. Initially, all persons with a special reimbursement for PD drugs were identified from the Special Reimbursement Register, after which those with potential PD misdiagnosis were excluded. The proportion of excluded persons (25.9%) is in line with that in previous studies of incorrect diagnoses. Data on drug use was derived from the Prescription Register since 1995. The incidence of muscle relaxant use was investigated from four years before to four years after PD diagnosis and compared to those without PD. Studies II and III were nested case-control studies wherein a three-year lag period was applied in exposure assessment, and the associations were investigated with conditional logistic regression adjusted for potential confounders. In Study III, the dose-response relationship was investigated by calculating cumulative and average annual exposure to inhaled β2AR agonists with quartiles of defined daily doses (DDDs) among users, and the lowest quartile was used as reference.

In Study I, the incidence of muscle relaxant use was higher among persons with PD from three years before PD diagnosis until six months after diagnosis. In Study II, DMARDs displayed no association with PD risk except for chloroquine/hydroxychloroquine, which was associated with reduced PD risk when compared to nonuse (odds ratio 0.74; 95% confidence interval 0.56-0.97). In Study III, compared to nonuse, inhaled β2AR agonists lacked any association with PD risk. In dose-response analyses, only the highest quartile of annual exposure to long-acting β2AR agonists was associated with reduced PD risk. This association was modified by pulmonary diagnosis type, and the lowest risk estimates were observed among those with both asthma and COPD diagnoses.

The higher incidence of muscle relaxant use before PD diagnosis probably reflects the progression of prodromal motor symptoms and underlines the importance of choosing appropriate exposure assessment period for risk factor studies. Overall, DMARDs did not modify PD risk in persons with RA; however, further studies are needed to confirm findings for chloroquine/hydroxychloroquine. As for inhaled β2AR agonists, the findings in this thesis do not support their risk-reducing potential in PD. Reduced PD risk, which emerged in dose-response analyses, could be due to pulmonary disease severity and residual confounding by smoking.

Keywords: Parkinson's disease, risk factors, pharmacoepidemiology, prodromal symptoms, drugs, registers, case-control studies

Paakinaho, Anne
Reumalääkkeiden ja inhaloitavien beeta-2 agonistien yhteys Parkinsonin taudin riskiin – valtakunnallinen rekisteritutkimus
Kuopio: Itä-Suomen yliopisto
Publications of the University of Eastern Finland
Dissertations in Health Sciences 803. 2024, 161 s.
ISBN: 978-952-61-5094-9 (nid.)
ISSNL: 1798-5706
ISSN: 1798-5706
ISBN: 978-952-61-5095-6 (PDF)
ISSN: 1798-5714 (PDF)

TIIVISTELMÄ

Parkinsonin taudin syntyperä on edelleen epäselvä aktiivisesta tutkimuksesta huolimatta. Ikä on Parkinsonin taudin tärkein riskitekijä, mutta muokattavissa olevista riskitekijöistä tarvitaan lisätietoa. Lääkkeet Parkinsonin taudin riskitekijöinä on kiinnostava tutkimuskohde, sillä tunnistamalla pienempään sairastumisriskiin liittyviä lääkkeitä voidaan edistää uusien hoitojen kehitystä. Tieto näiden lääkkeiden vaikutusmekanismeista voi paljastaa Parkinsonin taudin kehittymiseen liittyviä molekulaarisia mekanismeja. Riskitekijätutkimusten haasteena on kuitenkin pitkä diagnoosia edeltävä prodromaalivaihe, jolloin taudin kehittyminen on jo alkanut, mutta esiintyvät oireet eivät vielä täytä Parkinsonin taudin diagnostisia kriteereitä.

Tämän väitöskirjatutkimuksen tavoitteena oli selvittää, ovatko reumalääkkeet ja astman ja keuhkoahtaumataudin hoidossa käytettävät inhaloitavat beeta-2 agonistit yhteydessä Parkinsonin taudin riskiin. Nivelreuma on yhdistetty alhaisempaan Parkinsonin taudin riskiin, mikä voisi selittyä reumalääkkeiden käytöllä, koska ne muuntavat immuunivastetta. Reumalääkkeitä on kuitenkin tutkittu Parkinsonin taudin yhteydessä hyvin vähän. Kokeellisten tutkimusten mukaan beeta-2 agonistit voivat vähentää Parkinsonin taudin kannalta oleellisen alfa-

synukleiini proteiinin ilmentymistä. Lääke-epidemiologiset tutkimustulokset ovat olleet kuitenkin ristiriitaisia.

Osatyössä I selvitettiin mielekästä lääkealtisteen arviointijaksoa tutkimalla lihasrelaksanttien käytön ilmaantuvuutta merkkinä lihasoireiden puhkeamisesta ennen diagnoosia. Näin pystyttiin vähentämään käänteisen syy-seuraussuhteen riskiä osatöissä II ja III. Mahdollista hoitoaihesekoittuneisuutta vähennettiin tutkimalla lääkealtisteen ja Parkinsonin taudin riskin välistä yhteyttä käyttöaiheeseen rajatussa tutkimusasetelmassa. Osatyö II rajattiin nivelreumaa sairastaviin ja osatyö III henkilöihin, joilla oli joko astman tai keuhkoahtaumataudin diagnoosi.

Väitöskirjatutkimus perustui rekisteripohjaiseen FINPARK (Finnish Parkinson's disease study) -kohorttiin, joka kattaa kotona asuvat vuosina 1996–2015 Parkinsonin taudin diagnoosin saaneet henkilöt ja heille iän, sukupuolen ja sairaanhoitopiirin mukaan kaltaistetut verrokkihenkilöt. Kaikki Parkinsonin taudin lääkkeille erityiskorvausoikeuden saaneet henkilöt tunnistettiin Kelan erityiskorvausoikeusrekisteristä, jonka jälkeen poissuljettiin ne, joilla oli mahdollinen virhediagnoosi (25,9 %). Poissuljettujen henkilöiden osuus on samankaltainen kuin mahdollisten virhediagnoosien määrä aiemmissa tutkimuksissa. Tieto lääkeostoista kerättiin Kelan reseptitiedostosta vuodesta 1995 alkaen. Lihasrelaksanttien käytön ilmaantuvuutta tutkittiin neljä vuotta ennen ja jälkeen Parkinsonin taudin diagnoosin ja verrattiin vertailuhenkilöihin, joilla ei ollut Parkinsonin tautia. Osatyöt II ja III olivat upotettuja tapaus-verrokkitutkimuksia, joissa huomioitiin ainoastaan ainakin kolme vuotta ennen indeksipäivää tapahtunut lääkealtistus. Suhteellinen riski arvioitiin ehdollisella logistisella regressiolla ja malli vakioitiin mahdollisilla sekoittavilla tekijöillä. Osatyössä III arvioitiin annos-vastesuhde määrittämällä kumulatiivisen ja keskimääräisen vuosittaisen altistuksen kvartiilit määriteltyjen vuorokausiannosten avulla inhaloitavien beeta-2 agonistien käyttäjille.

Osatyössä I lihasrelaksanttien käytön ilmaantuvuus oli suurempaa Parkinsonin tautia sairastavilla kolme vuotta ennen diagnoosihetkeä jatkuen puoli vuotta sen jälkeen. Osatyössä II reumalääkkeet eivät olleet yhteydessä Parkinsonin taudin riskiin verrattuna henkilöihin, jotka eivät olleet käyttäneet kyseisiä lääkkeitä lukuun ottamatta

klorokiinia/hydroksiklorokiinia (vetosuhde 0,74; 95 % luottamusväli 0,56–0,97). Osatyössä III inhaloitavat beeta-2 agonistit eivät olleet yhteydessä Parkinsonin taudin riskiin verrattuna henkilöihin, jotka eivät käyttäneet näitä lääkkeitä. Annos-vasteanalyyseissa ainoastaan pitkävaikutteisten beeta-2 agonistien keskimääräisen vuosittaisen altistuksen korkein kvartiili oli yhteydessä pienempään Parkinsonin taudin riskiin. Keuhkosairauden tyyppi muokkasi yhteyttä, ja alin suhteellinen riski havaittiin henkilöillä, joilla oli sekä astman ja keuhkoahtaumataudin diagnoosit.

Lihasrelaksanttien käytön suurempi ilmaantuvuus todennäköisesti heijastaa motoristen oireiden kehittymistä ennen diagnoosia, ja korostaa asianmukaisen arviointijakson valinnan tärkeyttä riskitekijätutkimuksissa. Reumalääkkeet eivät yleisesti ottaen vaikuttaneet Parkinsonin taudin riskiin nivelreumaa sairastavilla, mutta lisätutkimuksia kuitenkin tarvitaan varmistamaan löydös klorokiinin/hydroksiklorokiinin osalta. Tämän väitöskirjan tulosten perusteella beeta-2 agonistit eivät vaikuta suojaavan Parkinsonin taudilta. Annos-vasteanalyyseissä näkynyt alhaisempi Parkinsonin taudin riski voi selittyä keuhkosairauden vakavuusasteella ja tupakoinnin aiheuttamalla jäännössekoittuneisuudella.

Avainsanat: Parkinsonin tauti, riskitekijät, lääke-epidemiologia, prodromaalioireet, lääkkeet, rekisterit, tapaus-verrokkitutkimukset

ACKNOWLEDGEMENTS

This research was conducted at the School of Pharmacy, University of Eastern Finland, during 2018-2023. The first step into the project and becoming familiar with pharmacoepidemiology was in autumn 2018 when I started my master's thesis, which turned out to be Study I of my doctoral thesis. I am extremely grateful for the financial support from the Michael J. Fox Foundation, the Finnish Parkinson Foundation, and the Doctoral Programme in Drug Research at the University of Eastern Finland; this support enabled me to continue with and complete this thesis during 2020-2023.

Above all, I am grateful to my main supervisor, Professor Anna-Maija Tolppanen: firstly, for entrusting me with the project and, secondly, for her strong support, guidance, and pharmacoepidemiological expertise. I also owe my gratitude to my other supervisors, Professor Emerita Sirpa Hartikainen, Docent Miia Tiihonen, and Docent Marjaana Koponen, for their invaluable insights and knowledge. I also want to thank the clinical expertise provided by Professors Markku Kauppi and Heikki Koskela and other co-authors: Docent Heidi Taipale, Niina Karttunen, and Professor Jari Tiihonen for their contribution. I wish to thank Professor Mika Gissler and Associate Professor Björn Pasternak for reviewing this thesis. I also want to express my gratitude to Professor Olaf Klungel for accepting the invitation to be my opponent in the public examination.

I am grateful for getting to be part of the Real-World Evidence Team. Special thanks to my colleagues that I had the pleasure of sharing the office with for some time: Mai Vu and Shin Liau; thank you for the conversations. I also owe thanks to Blair Rajamaki, Barkat Babar, and Isabell Rumrich for memories created both at and outside of work. I found some other new friends along the way, and I will greet you with a smile when we meet again.

I have always been keen on doing sports; academic support apart, this thesis would have never been conducted without exercising. Regarding university life, it was great to be part of the Pharmacy staff team in the

floorball games with pharmacy students. I also experienced one of the best badminton games ever with people from the Biopharmacy discipline. Outside of university, I am grateful for the Puijo skiing tracks, the wonderful orienteering forests of Kuopio, and the Kuopio Ju-jitsu club, for unforgettable experiences.

The period of conducting this thesis research was anything but easy. The COVID-19 pandemic forced us to work from home office in March 2020, just when I was able to continue with the project. The shadow of COVID-19 followed for a long period and narrowed the possibilities to experience live conferences, among others. In addition to the pandemic, many personal setbacks kept on coming. I would even say that conducting the research itself was somewhat straightforward compared to everything else. However, everything in life is temporary, including troubles.

Finally, I want to thank my family and friends for the company and activities beyond this thesis; that support helped clarify my thoughts during the journey. A special thanks goes to my late father: you taught me countless things, for which I am forever grateful.

Kuopio, December 2023
Anne Paakinaho

LIST OF ORIGINAL PUBLICATIONS

This dissertation is based on the following original publications:

I Paakinaho, A., Karttunen, N., Koponen, M., Taipale, H., Tolppanen, A.-M., Hartikainen, S., Tiihonen, M., 2020. Incidence of muscle relaxant use in relation to diagnosis of Parkinson's disease. Int J Clin Pharm 42, 336–340.

II Paakinaho, A., Koponen, M., Tiihonen, M., Kauppi, M., Hartikainen, S., Tolppanen, A.-M., 2022. Disease-modifying antirheumatic drugs and risk of Parkinson disease: nested case-control study of people with rheumatoid arthritis. Neurology 98, e1273–e1281.

III Paakinaho, A., Tiihonen, M., Koskela, H., Koponen, M., Tiihonen, J., Hartikainen, S., Tolppanen, A.-M., 2023. β2-adrenoceptor agonists in asthma or chronic obstructive pulmonary disease and risk of Parkinson's disease: nested case-control study. Clin Epidemiol 15, 695–705.

CONTENTS

ABBREVIATIONS

6-OHDA	6-hydroxydopamine
ACPA	Anti-citrullinated protein antibody
AD	Alzheimer's disease
aOR	Adjusted odds ratio
ATC	Anatomical therapeutic chemical
CI	Confidence interval
COMT	Catechol-O-methyltransferase
COPD	Chronic obstructive pulmonary disease
DDD	Defined daily dose
DMARD	Disease-modifying antirheumatic drug
FINPARK	Finnish Parkinson's disease study
GP	General practitioner
HIF-1	Hypoxia-inducible factor-1
HR	Hazard ratio
ICD	International classification of diseases
IL-6	Interleukin-6
IMDH	Inosine monophosphate dehydrogenase
IR	Incidence rate
IRR	Incidence rate ratio
LRRK2	Leucine-rich repeat kinase 2
MAO-B	Monoamine oxidase-B
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MR	Mendelian randomization
MRI	Magnetic resonance imaging
NSAID	Nonsteroidal anti-inflammatory drug
OR	Odds ratio

PD	Parkinson’s disease
RA	Rheumatoid arthritis
RR	Rate ratio
SD	Standard deviation
SII	Social Insurance Institution
SIR	Standardized incidence ratio
SNCA	Synuclein alpha
SNP	Single nucleotide polymorphism
TNF	Tumour necrosis factor
UKPDSBB	United Kingdom Parkinson’s Disease Society Brain Bank
WHO	World Health Organization
β2AR	β2-adrenoceptor

1 INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by loss of dopaminergic neurons (Poewe et al., 2017). The prodromal stage can last for years, during which the neuropathology progresses, and different non-motor and motor symptoms start to occur before clinical motor symptoms meet diagnostic criteria. Despite active research, the understanding of PD aetiology is incomplete; the primary risk factor is age (Pang et al., 2019). Several other risk factors have been investigated, but the literature is inconsistent (Belvisi et al., 2020). Although symptomatic treatments exist, recent therapeutic advances have been modest; better understanding of risk factors could help identify preventive actions (Bloem et al., 2021; Chen, 2018). In addition, pharmacoepidemiological studies on drugs associated with lower PD risk could be one approach to identify candidates for drug repurposing, identifying new purposes for already existing drugs (Cepeda et al., 2019; Courtois et al., 2022; Koponen et al., 2022).

This thesis focused on drugs that could reduce PD risk. Disease-modifying antirheumatic drugs (DMARDs) may contribute to lower PD risk in persons with rheumatoid arthritis (RA), due to their immunomodulatory effects (Gonzalez-Latapi and Marras, 2022). However, previous studies have left unexplored how specific DMARDs in persons with RA are associated with PD risk. β2-adrenoceptor (β2AR) agonists have drawn attention due to their neuroprotective effects in experimental PD models (Mittal et al., 2017; Peterson et al., 2014). Recent register-based studies have suggested β2AR agonists have potential in drug repurposing for PD (Cepeda et al., 2019; Courtois et al., 2022). Despite the increasing number of epidemiological studies, findings for β2AR agonists have been inconsistent (Singh et al., 2022).

Pharmacoepidemiological studies on PD risk factors are challenged by confounding by indication, meaning that the underlying indication for drug use is also related to PD risk. An additional challenge is posed by PD prodromal symptoms, which can lead to reverse causality. Reverse

causality refers to a situation wherein a drug seems to be associated with PD risk, but drug use is affected by PD prodromal symptoms. As PD develops gradually, capturing exposure several years before diagnosis is important. The use of register-based data avoids recall bias, a problem in self-reported exposure. Finnish prescription and health care registers provide a comprehensive data source for pharmacoepidemiological studies. The long history of these registers and data linkage enabled us to examine multiple exposures and gather information on several potential confounders.

This thesis assessed whether DMARDs and inhaled β2AR agonists were associated with lower PD risk in indication-restricted study designs. These studies were conducted within the nationwide register-based Finnish Parkinson's disease study (FINPARK) of 22,189 community-dwelling residents of Finland who received a clinically verified PD diagnosis during 1996-2015. To identify the relevant exposure assessment period for these risk factor studies, the incidence of muscle relaxant use as proxy for prodromal muscle symptoms was investigated.

2 REVIEW OF THE LITERATURE

2.1 PARKINSON'S DISEASE

PD is a fast-growing neurological condition, and it is the most common movement disorder (Bloem et al., 2021; Pang et al., 2019). Cardinal motor features comprise bradykinesia, rest tremor, rigidity, and postural instability (Jankovic and Tan, 2020). Disease aetiology is largely unknown, but interaction between ageing, genetics, and environmental factors is probably involved (Pang et al., 2019).

PD is an age-related disease, and its prevalence and incidence increase with age (Hirsch et al., 2016; Pringsheim et al., 2014). Mean onset age is about 70 according to a meta-analysis of population-based incidence studies (Macleod et al., 2018). Globally, in 2016, 6.1 million had PD (GBD 2016 Parkinson's Disease Collaborators, 2018). PD incidence and prevalence have increased globally, and the number of people with PD has more than doubled in two decades (Dorsey et al., 2018). This rise might be partly explained by population ageing and increased longevity (Bloem et al., 2021).

The exact number of persons with PD in Finland is unknown, but over 18,000 were eligible for special reimbursement for PD drugs at the end of 2021 (Sipilä and Kaasinen, 2022). In Finland, the proportion of those who received a special reimbursement for PD drugs among all persons aged 35 and over increased from 0.044% to 0.056% during 1996-2016 (Anttila et al., 2020). This increase probably reflects the ageing population in Finland.

2.1.1 Pathophysiology

PD has a complex and widespread pathology, making it a heterogeneous disease (Bloem et al., 2021). Traditionally, pathological hallmarks are the accumulation of aggregated α-synuclein in Lewy bodies and Lewy neurites as well as gradual loss of dopamine cells in the s*ubstantia nigra pars compacta* (Jankovic and Tan, 2020). These processes lead to basal ganglia dysfunction and appearance of typical motor symptoms. Some other regions of the nervous system and other neurotransmitter systems implicated in various non-motor symptoms of PD, are also affected (Schapira et al., 2017). In addition to α-synuclein, other molecular and cellular processes, such as mitochondrial dysfunction, neuroinflammation, and oxidative stress, are also involved (Jankovic and Tan, 2020). The interplay of these processes can be complex, and various mechanisms can contribute to neuronal death.

α-synuclein is a small neuronal protein predominantly expressed in the brain (Burré, 2015). The understanding of the normal function of this protein is incomplete, but it can have a role in vesicular transport and neurotransmitter release (Angot et al., 2010). α-synuclein is natively unfolded; in its misfolded form, it becomes insoluble and starts to aggregate with other pathologically misfolded α-synuclein proteins, becoming toxic (Braak et al., 2004; Poewe et al., 2017). The initial trigger of aggregation is unknown; reasons include overproduction of the protein, mutations in PD-related genes, and disrupted protein degradation (Poewe et al., 2017). Misfolded α-synuclein is the primary component of Lewy bodies and Lewy neurites (Goedert et al., 2013). Dopaminergic neurons in the *substantia nigra pars compacta* are especially vulnerable to α-synuclein pathology in PD (Minakaki et al., 2020).

Although the essential brain region in PD is the *substantia nigra pars compacta*, the pathology probably begins elsewhere. The site of origin for α-synuclein pathology is debated. Gradual propagation of pathology and progression of symptoms could be explained by the Braak hypothesis, according to which progression can be divided into six stages (Braak et al., 2004). In stages I and II, α-synuclein pathology is present in the lower brain

stem and olfactory regions. The first sites of α-synuclein aggregation could also be in the gut enteric nerves, from where it could move via the vagal nerve towards the brain (Goedert et al., 2013). In stages III and IV, the pathology ascends to the midbrain, especially causing the death of dopaminergic neurons in the *substantia nigra pars compacta* when typical motor symptoms also appear (Braak et al., 2004). Then, in stages V and VI, the process finally enters the neocortex. The Braak hypothesis has been debated since PD clinical severity might not always relate to these Braak stages (Burke et al., 2008).

Recently, the body-first versus brain-first model was proposed (Horsager et al., 2020). In the body-first subtype, pathology originates in the enteric or peripheral autonomic nervous system, after which it ascends to the central nervous system via the vagus nerve and sympathetic connectome. However, in the brain-first subtype, α-synuclein pathology primarily originates in the brain itself, probably in the amygdala, or sometimes secondarily via the olfactory bulb, later descending to the peripheral autonomic nervous system. This body-first versus brain-first hypothesis could explain why persons with PD can have different clinical phenotypes—for example, variation in non-motor symptoms (Borghammer, 2021). Regardless of where the pathology originates, α-synuclein could propagate in a prion-like manner (Angot et al., 2010). Misfolded α-synuclein can spread between cells and trigger aggregation in a new cell and cause cell death while it spreads. Thus, initial misfolding in only a small number of cells can lead to progressive spreading and explain why α-synuclein pathology includes multiple regions (Poewe et al., 2017).

The main pathophysiological processes involve functional changes in basal ganglia circuitry due to dopamine depletion (Magrinelli et al., 2016). The function of the basal ganglia is imbalanced due to decreased dopamine transmission in the striatum because of the loss of dopaminergic neurons in the *substantia nigra pars compacta*. These changes produce imbalance between direct and indirect pathways through the basal ganglia, by increasing the activity of the indirect pathway over the direct one, which leads to over-inhibition of thalamocortical and brainstem motor systems. According to the literature, by the time clinical motor

symptoms are evident, approximately 50% of dopaminergic neurons have died in the *substantia nigra pars compacta*, which implies that neurodegeneration begins long before diagnosis (Cheng et al., 2010).

Inflammation and immune system dysfunction have been connected to PD pathophysiology (Tan et al., 2020). Some examples of linking mechanisms are activated microglia (the primary immune cells in the central nervous system), increased levels of pro-inflammatory cytokines, as well as changes in the function of innate and adaptive immune cells. The exact mechanisms between neuroinflammation and PD are unknown.

2.1.2 Clinical symptoms

PD is characterized as a movement disorder (Berg et al., 2021). Still, persons with PD also experience a wide range of non-motor symptoms, which can be the first ones to emerge and may precede diagnosis by 10-20 years. Persons with PD exhibit variation in symptoms and in their sequence of appearance and progression (Jankovic, 2008; Poewe et al., 2017); for a schematic view of symptom onset, see Figure 1.

PD progression is divided into three stages (Berg et al., 2015). In preclinical PD, neurodegeneration has begun but with no symptoms or signs present. In prodromal PD, different kinds of symptoms and signs start to appear, but they are not distinguishable as PD. In clinical PD, diagnosis is possible due to the presence of typical motor symptoms.

Most prodromal symptoms are non-motor ones, including constipation, rapid eye movement sleep behaviour disorder, depression, and olfactory deficits such as hyposmia (Schapira et al., 2017). Non-motor problems continue to appear throughout disease progression and are not limited to the prodromal stage. While PD progresses, the burden of non-motor symptoms increases. Some non-motor symptoms, for example anxiety and depression, can occur from the prodromal stage to the late stages of the disease and fluctuate according to motor state. Various other potential non-motor features exist. Pain is common in PD and can appear anytime during the disease, often preceding diagnosis (Antonini et al., 2018). Apathy and fatigue are distinct clinical symptoms; both can emerge in early stages

of the disease (Schapira et al., 2017). On the contrary, cognitive decline and dementia; psychotic symptoms, mainly visual hallucinations; as well as some autonomic problems such as orthostatic hypotension and urinary dysfunction are more prevalent at later disease stages. No non-motor symptom is specific to PD.

Subtle motor signs that do not meet diagnostic criteria may precede clinical PD; examples are stiffness, tremor, and feeling of imbalance (de Lau et al., 2006; Maetzler and Hausdorff, 2012). The onset of classic motor features such as bradykinesia, rigidity, and rest tremor enables clinical diagnosis (Jankovic, 2008; Tolosa et al., 2021). Bradykinesia is the most characteristic clinical feature of PD and refers to general slowness of movements. Rigidity means increased resistance to the passive movement of the joint. Rest tremor in PD is unilateral and has a 4-6 Hz amplitude, usually involving the so-called pill-rolling tremor of the hands. Postural instability refers to impaired adjustments in a person's ability to change or maintain postures. Freezing, along with postural instability, typically occurs at later stages. Freezing causes sudden inability to move feet forward when initiating gait, during gait, or when turning or going through narrow spaces. Both postural instability and freezing are common causes of falls. Fall risk is increased even before diagnosis and not merely in the advanced stage (Nyström et al., 2016). Axial posture deformities may occur due to rigidity and can result, for example, in flexed neck and trunk posture later in the disease (Jankovic, 2008).

Motor symptoms can initially be managed with dopaminergic therapy; however, as PD advances, motor fluctuations are more apparent due to complications of long-term levodopa therapy and drug-induced dyskinesias, i.e., involuntary movements can occur (Magrinelli et al., 2016). Advancing non-motor symptoms together with worsening motor symptom control contribute to progressive disability.

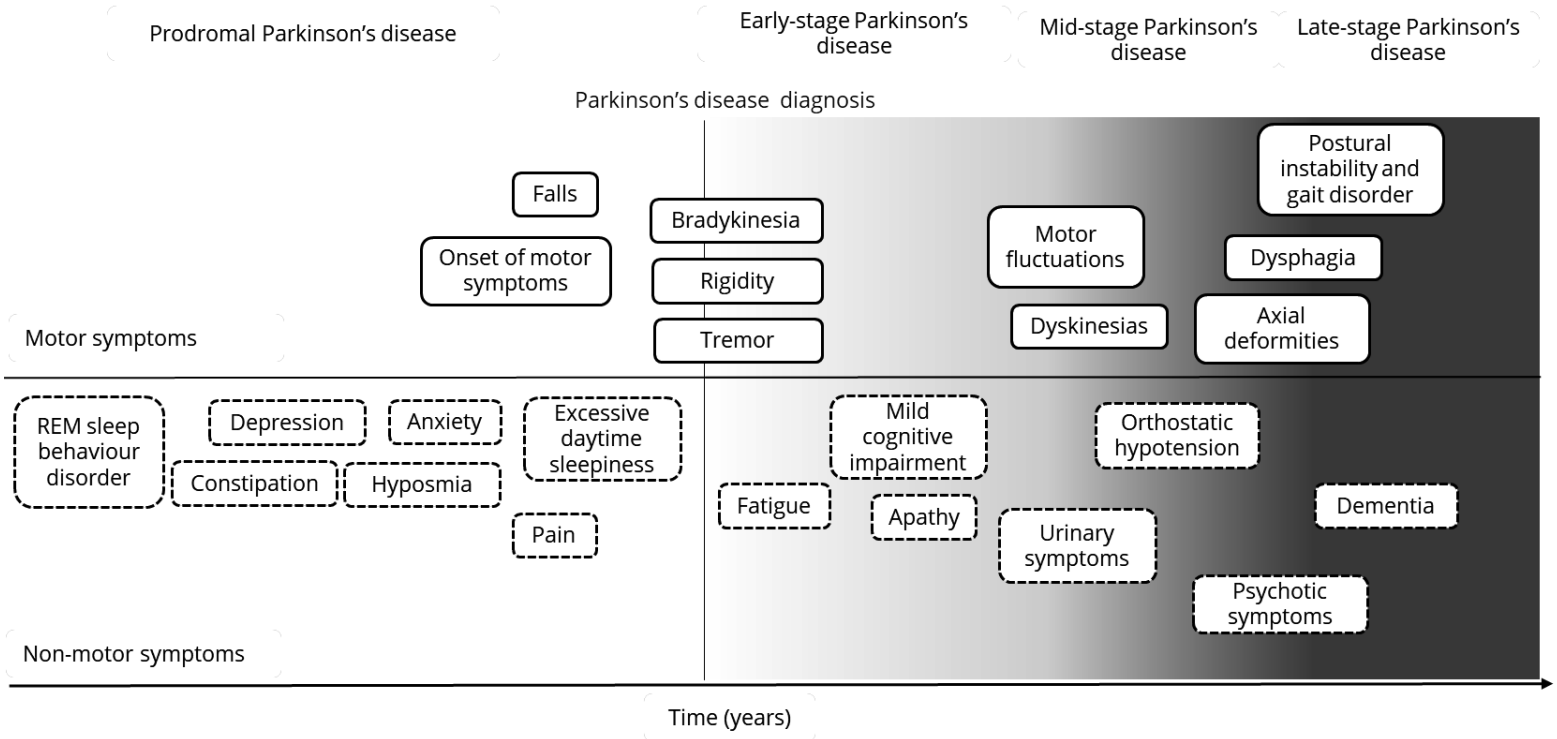


Figure 1. A schematic summary of the appearance of various non-motor and motor symptoms during the course of Parkinson's disease. Modified from Poewe et al., 2017. Individuals vary in the order of symptom appearance and symptom fluctuation.

2.1.3 Pharmacotherapy for motor symptoms

PD treatment is only symptomatic, with no disease-modifying treatments available currently (Armstrong and Okun, 2020). The treatment of motor symptoms is based on dopamine replacement therapy (Table 1). Pharmacotherapy is initiated if, due to motor symptoms, persons with PD experience disability or worsened quality of life (Parkinson's disease: Current Care Guidelines, 2022). The choice of initial treatment and therapy throughout the course of the disease must be individualized to the patient (Armstrong and Okun, 2020).

Table 1. Drugs commonly used in the treatment of motor symptoms in Parkinson's disease. (Connolly and Lang, 2014; Jankovic and Tan, 2020; Parkinson's disease: Current Care Guidelines, 2022).

Drug category	**Drugs or drug combinations**	**Potential adverse effects**
Levodopa and aromatic acid decarboxylase inhibitor	Levodopa-benserazide, levodopa-carbidopa	Nausea, orthostatic hypotension, hallucinations, dyskinesia
Dopamine agonists (non-ergot)	Pramipexole, ropinirole, rotigotine, apomorphine	Nausea, orthostatic hypotension, hallucinations, excessive sleepiness, impulse control disorder, dyskinesia
Monoamine oxidase-B (MAO-B) inhibitors	Rasagiline, selegiline	Nausea, dizziness, headache, exacerbation of levodopa adverse effects
Catechol-O-methyltransferase (COMT) inhibitors	Entacapone, opicapone	Nausea, diarrhoea, urine discoloration, exacerbation of levodopa adverse effects
Amantadine	Amantadine	Hallucinations, confusion, nausea, ankle oedema
Anticholinergics	Trihexyphenidyl, biperiden	Hallucinations, cognitive impairment, nausea, dry mouth, blurred vision, constipation, urinary retention

Since the 1960s, the most efficient treatment for motor symptoms has been levodopa, a precursor to dopamine (Table 1) (Fahn, 2008). Levodopa is decarboxylated to dopamine already in the peripheral tissues; however, unlike levodopa, peripherally administered dopamine cannot cross the blood-brain barrier. To increase bioavailability in the brain, levodopa is used in combination with aromatic acid decarboxylase inhibitors that prevent its peripheral metabolism into dopamine. Another catabolic route for levodopa and dopamine is 3-O-methylation. Combination with catechol-O-methyltransferase (COMT) inhibitors further prevents levodopa metabolism into 3-O-methyldopa, increases plasma levels, and prolongs dopaminergic stimulation (Schapira et al., 2009). Tolcapone differs from the two other available COMT inhibitors in that it can cross the blood-brain barrier and block levodopa degradation also in the brain (Artusi et al., 2021). However, hepatotoxicity concerns have limited its use (Artusi et al., 2021); currently, tolcapone preparations are not marketed in Finland (FimeaWeb, 2023).

Other dopaminergic drugs include monoamine oxidase-B (MAO-B) inhibitors that prolong the synaptic availability of dopamine in the striatum by inhibiting its metabolism as well as dopamine agonists that stimulate dopamine receptors (Table 1) (Poewe et al., 2017). Dopamine agonists were initially ergot-derived ones, such as cabergoline and bromocriptine but, due to adverse events such as heart valve abnormalities (Simonis et al., 2007; Tolosa et al., 1998), they were replaced by non-ergot preparations (Parkinson's disease: Current Care Guidelines, 2022). Both MAO-B inhibitors and dopamine agonists can also be used as adjunct therapy with levodopa (Fahn, 2008; Poewe, 1998).

Other antiparkinsonian drugs exist (Table 1). Anticholinergics were the first drugs to alleviate motor symptoms before dopaminergic drugs became available; their effect is presumed to be based on counteracting the imbalance between striatal dopamine and acetylcholine levels (Katzenschlager et al., 2003). Studies on anticholinergic use in PD were conducted years ago and fail to meet current requirements. These drugs may modestly alleviate motor symptoms, but their use is limited by adverse events such as risk of confusion. An anti-influenza drug,

amantadine, can be used to alleviate levodopa-induced dyskinesias (Rascol et al., 2021); however, a 2003 Cochrane review stated that evidence of its efficacy is insufficient (Crosby et al., 2003).

Initial PD therapy depends on symptom severity and age. According to Finnish Current Care Guidelines for Parkinson's disease, for persons below 60-65, initiation with a MAO-B inhibitor or dopamine agonist is recommended, unless the patient is multimorbid and has cognitive symptoms or severe motor symptoms (Parkinson's disease: Current Care Guidelines, 2022). In these cases, levodopa could be considered. For persons above 60-65, treatment can be initiated with levodopa. Previously in Finland, compared to that in current guidelines, the age recommendation for levodopa initiation was higher (>70) (Keränen and Marttila, 2002).

Advancing disease and long-term levodopa use eventually induce adverse effects including motor fluctuations and dyskinesias, i.e., involuntary movements (Armstrong and Okun, 2020; Jankovic, 2005). After 4-6 years of levodopa therapy, motor fluctuations and dyskinesias are present approximately in 40% of persons with PD (Ahlskog and Muenter, 2001). Motor fluctuations are related to response level to levodopa and refer to alterations between "on" periods with a good response and "off" periods, when drug effects have worn off and motor symptoms re-emerge (Espay et al., 2018; Fox and Lang, 2008; Jankovic, 2005). Dyskinesias are related to dopamine receptor stimulation. Peak-dose dyskinesia is the most common form, involving stereotypic, choreic, or ballistic movements of the head, trunk, and limbs; it appears during the highest drug concentrations. Dyskinesia can also occur during off-periods wherein symptoms are mainly dystonic, causing muscle contractions particularly in the legs and feet. Diphasic dyskinesia is less common and related to the beginning or end of levodopa dose. Higher doses, long disease duration, and young age of disease onset increase the risk of levodopa-related adverse effects (Schrag and Quinn, 2000; Wickremaratchi et al., 2009). Thus, when to initiate levodopa treatment has been a matter of debate, and delaying its use may avoid motor fluctuations and dyskinesias (de Bie et al., 2020; Kieburtz, 2008). However, recently a levodopa-sparing strategy

has appeared less necessary since it seems that motor fluctuations and dyskinesias emerge regardless of levodopa initiation timing (de Bie et al., 2020). In a randomized trial, compared to initiation with a dopamine agonist or MAO-B inhibitor, early levodopa initiation, despite dyskinesia appearance, led to a better health-related quality of life (PD MED Collaborative Group et al., 2014).

Noteworthily, unless symptoms are linked to motor fluctuations, non-motor symptoms unrelated to dopamine deficiency are unaffected by dopamine replacement therapy (Chaudhuri and Schapira, 2009; Schapira et al., 2017). By contrast, dopaminergic treatment can also induce non-motor symptoms such as visual hallucinations. The use of antiparkinsonian drugs is then reduced or discontinued (Connolly and Lang, 2014).

2.1.4 The diagnosis of Parkinson's disease

PD diagnosis is based on clinical evaluation and identification of classical symptoms (Parkinson's disease: Current Care Guidelines, 2022). United Kingdom Parkinson's Disease Society Brain Bank (UKPDSBB) criteria are used in Finland, and diagnosis is performed by a neurologist (Table 2) (Gibb and Lees, 1988; Parkinson's disease: Current Care Guidelines, 2022). Person diagnosed as having PD must have bradykinesia and at least one of the following symptoms: rigidity, rest tremor, or postural instability. Additionally, UKPDSBB criteria include exclusion and supportive positive criteria for PD diagnostics. For UKPDSBB criteria, a meta-analysis reported a pooled diagnostic accuracy of 82.7% (Rizzo et al., 2016).

Table 2. United Kingdom Parkinson's Disease Society Brain Bank clinical diagnostic criteria for idiopathic Parkinson's disease (Gibb and Lees, 1988; Parkinson's disease: Current Care Guidelines, 2022).

	Criteria
Step 1	Diagnosis of Parkinsonian syndrome
	Bradykinesia and At least one of the following: a) Muscular rigidity b) 4–6 Hz rest tremor c) Postural instability that is not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction
Step 2	Exclusion criteria for Parkinson's disease
	1. History of repeated strokes with stepwise progression of Parkinsonian features 2. History of repeated head injury 3. History of definite encephalitis 4. Oculogyric crises 5. Neuroleptic treatment at symptom onset 6. More than one affected relative[1] 7. Sustained remission 8. Strictly unilateral features after 3 years 9. Supranuclear gaze palsy 10. Cerebellar signs

Table 2 (continued)

Step 2	Exclusion criteria for Parkinson's disease 11. Early severe autonomic involvement 12. Early severe dementia with disturbances of memory, language, and praxis 13. Babinski sign 14. Presence of cerebral tumour or communicating hydrocephalus on brain imaging 15. Negative response to large levodopa doses
Step 3	Supportive prospective positive criteria for Parkinson's disease
	1. Unilateral onset 2. Rest tremor present 3. Progressive disorder 4. Persistent asymmetry affecting side of onset most 5. Excellent response (70-100%) to levodopa 6. Severe levodopa-induced chorea 7. Levodopa response for 5 years or more 8. Clinical course of 10 years or more

[1]Criteria are for identifying idiopathic Parkinson's disease and not the familial form of Parkinson's disease (Kaasinen, 2017).
Exclusion of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) from exclusion criteria is according to Finnish Current Care Guidelines for Parkinson's disease.

Differential diagnosis may be challenging in the early stages of disease due to other conditions that mimic the clinical presentation of PD (Adler et al., 2021; Tolosa et al., 2006). Initial diagnosis may be later revised, and the direction of diagnostic switches can be either to or from PD (Caslake et al., 2008; Keshtkarjahromi et al., 2022). A study assessed changes in clinical diagnosis over time in a cohort of persons with incident parkinsonism, reporting that, in 22 persons (33%), initial diagnosis was changed after a median follow-up of 29 months, with most changes occurring during the first year (Caslake et al., 2008). The most common misdiagnoses for PD at early stage are essential tremor and different types of secondary parkinsonism including drug-induced parkinsonism and vascular parkinsonism as well as Alzheimer's disease (AD) and dementia with Lewy bodies (Caslake et al., 2008; Meara et al., 1999; Schrag et al., 2002). At early

stages, differentiating PD from atypical parkinsonian disorders, including multiple system atrophy, progressive supranuclear palsy, and corticobasal degeneration, is also challenging (Tolosa et al., 2021).

PD diagnosis is impossible based on neuroimaging which, however, can assist in differential diagnosis of PD (Politis, 2014). Magnetic resonance imaging (MRI) can be used to examine structural basal ganglia pathology and observe, for example, infarcts, haematomas, and iron deposition (Tolosa et al., 2021). Therefore, MRI can help identify secondary parkinsonism caused by structural lesions—for example, vascular parkinsonism and neoplasms (Politis, 2014). MRI can be helpful in measuring the degree and distribution of brain atrophy in persons with symptoms of atypical parkinsonian disorders. Dopamine transporter single-photon emission computed tomography scanning may aid in differentiating between nondegenerative parkinsonism and tremor disorders (for example, essential tremor) and degenerative parkinsonism (for example, PD and multiple system atrophy). However, it is unsuitable for differentiating further between degenerative causes of parkinsonism.

Genetic testing may serve to identify common known gene mutations but is not in routine use in Finland, and the decision to test is made individually (Parkinson's disease: Current Care Guidelines, 2022). Especially if a person under 40 experiences symptoms, mutations in recessively inherited genes (for example, *PRKN*) could be examined. Confirmation of genetic background can be valuable for the individual and help identify family members at risk (Cook et al., 2021).

A definitive diagnosis of PD can only be acquired in pathological examination post-mortem (Gelb et al., 1999). A Finnish study examined the diagnostic accuracy of different parkinsonism syndromes with pathological confirmation (Joutsa et al., 2014). An accuracy of 75.3% was reported for PD; 58 persons out of 77 that had received clinically verified PD diagnosis by neurologists were confirmed after neuropathological examination. Sensitivity for clinical diagnosis, i.e., correctly identifying all those with PD, was 89.2%. However, specificity, i.e., correctly identifying those who have no PD, was lower: 57.8%. Among those initially diagnosed with PD (n=77), the most common pathologically revised diagnoses were AD (n=5),

progressive supranuclear palsy (n=5), multiple system atrophy (n=4), and vascular parkinsonism (n=3). In another clinicopathological study, PD was erroneously diagnosed in 10 persons out of 100 (10%), and the most common neuropathological diagnoses were multiple system atrophy (n=6) and progressive supranuclear palsy (n=2) (Hughes et al., 2001). Diagnostic accuracy seems to be better after disease duration ≥5 years (89%) compared to less than 5 years (71%), with PD diagnosis verified by neuropathological examination (Adler et al., 2021).

2.2 MUSCLE RELAXANT USE RELATED TO PARKINSON'S DISEASE

Muscle symptoms

Persons with PD can experience different types of muscle symptoms. Musculoskeletal pain can originate from rigidity, stiffness, and reduced mobility (Ford, 2010) and is the most common type of pain in persons with PD, with a reported frequency of 40-75% (Tai and Lin, 2020). Musculoskeletal pain, especially shoulder pain, may precede PD but appear anytime during the disease (Ha and Jankovic, 2012; Stamey et al., 2008). In PD, some typical locations for muscle spasms are in the neck, arms, and paraspinal muscles and for joint pain in the shoulders, hips, and knees (Ford, 2010). Dystonia-related muscle spasms and pain occur later in the disease and are related to response to dopaminergic therapy (Ford, 2010).

In addition to typical motor symptoms of PD, nonspecific muscle symptoms seem to precede PD. Motor symptoms, especially tremor and balance impairment, may occur even 10 years before PD diagnosis (Bohlken et al., 2022; Schrag et al., 2022, 2015; Simonet et al., 2022). Stiffness or shoulder/neck pain, which can be indirect symptoms of rigidity, are more common in persons with PD 2-10 years before PD diagnosis. As motor symptoms develop gradually, years may pass before symptoms meet diagnostic criteria (Maetzler and Hausdorff, 2012).

Muscle relaxants

Centrally acting muscle relaxants are used in the treatment of spasticity commonly associated with upper motor neuron diseases such as multiple sclerosis, spinal cord injury, and stroke, or musculoskeletal conditions such as back or neck pain and muscle spasms (Chou et al., 2004; Witenko et al., 2014). They have variable mechanisms of action not exactly known. Antispasticity agents include baclofen, and antispasmodic agents include orphenadrine, chlorzoxazone, carisoprodol, methocarbamol, and tizanidine. The peripherally acting muscle relaxant, botulinum toxin, can be used to treat spasticity and dystonia (Jankovic, 2013; Picelli et al., 2019).

Orphenadrine is an analogue of the antihistamine diphenhydramine and has anticholinergic properties (Witenko et al., 2014). Despite analgesic effects on its own, it may be used in combination with paracetamol to relieve painful musculoskeletal conditions (McGuinness, 1983; Waldman, 1994). Before levodopa was introduced, anticholinergic drugs, including orphenadrine, were the first medications available for PD, and they alleviated mainly rigidity and resting tremor (Brocks, 1999; Hughes et al., 1971). Anticholinergics may correct the imbalance between dopaminergic and cholinergic neurotransmitter pathways that arises due to dopamine depletion in the striatum, which could explain motor symptom improvement (Brocks, 1999). According to a register-based study from New Zealand, orphenadrine use in PD gradually declined during 1995-2011 (Pitcher et al., 2014). Anticholinergic adverse effects such as urinary retention, constipation, confusion, as well as falls and related injuries, limit orphenadrine use in older adults, and American Geriatrics Society Beers Criteria® recommend avoiding its use in persons ≥65 (Brocks, 1999; By the 2023 American Geriatrics Society Beers Criteria® Update Expert Panel, 2023).

Tizanidine is an imidazoline derivative and centrally acting α2-adrenergic agonist (Wagstaff and Bryson, 1997). It causes presynaptic inhibition of motor neurons by inhibiting the release of excitatory amino acids from spinal interneurons (Ghanavatian and Derian 2023). Tizanidine is approved for treating muscle spasms and spasticity. Potential adverse effects include

dry mouth, drowsiness, dizziness, a prolonged QT interval, and hypotension.

Baclofen is a γ-aminobutyric acid B agonist that decreases synaptic spinal cord transmission (Ghanavatian and Derian, 2023b). Baclofen is used to manage spasticity and muscle spasms. Potential adverse effects include drowsiness, muscle weakness, nausea, and confusion. A 1970s study reported that baclofen treatment worsened functional capacity in levodopa-treated persons with PD (Lees et al., 1978). Baclofen is not recommended for persons with PD as we lack knowledge on its effects in PD (Ghanavatian and Derian, 2023b).

Currently, methocarbamol or chlorzoxazone are not marketed in Finland as their marketing authorisations were cancelled around the early 2000s (in 2001 for methocarbamol, 1999 for its combination preparation, and 2003 for chlorzoxazone) (FimeaWeb, 2023). Carisoprodol was withdrawn in 2007 according to the European Medicines Agency recommendation (EMA Press release, 2007). Its risks outweigh its benefits, and abuse and addiction, intoxication, and psychomotor impairment are potential risks.

To the best of our knowledge, no previous studies have systematically explored initiations of muscle relaxant use in relation to PD diagnosis. The use of muscle relaxants may be an indicator of various muscle symptoms that may occur in the prodromal stage. Dopaminergic therapy can alleviate PD-related musculoskeletal pain (Ha and Jankovic, 2012). However, particularly before PD is diagnosed, other treatment options may be more probably used to relieve nonspecific muscle symptoms.

2.3 RISK FACTORS OF PARKINSON'S DISEASE

2.3.1 Non-modifiable risk factors

Age

Non-modifiable risk factors for PD include age, sex, and genetics (Cerri et al., 2019; Pang et al., 2019). Age is the risk factor with the most robust association with PD although PD is not due to ageing (Pang et al., 2019). PD incidence increases with age in both men and women (Figure 2). In a meta-analysis including epidemiologic studies from 2001 to 2014, peak incidence for women was between 70-79; among men, the incidence rose even after 80 (Hirsch et al., 2016). In addition to age-related changes, the involvement of genetic and environmental factors is likely (Pang et al., 2019).

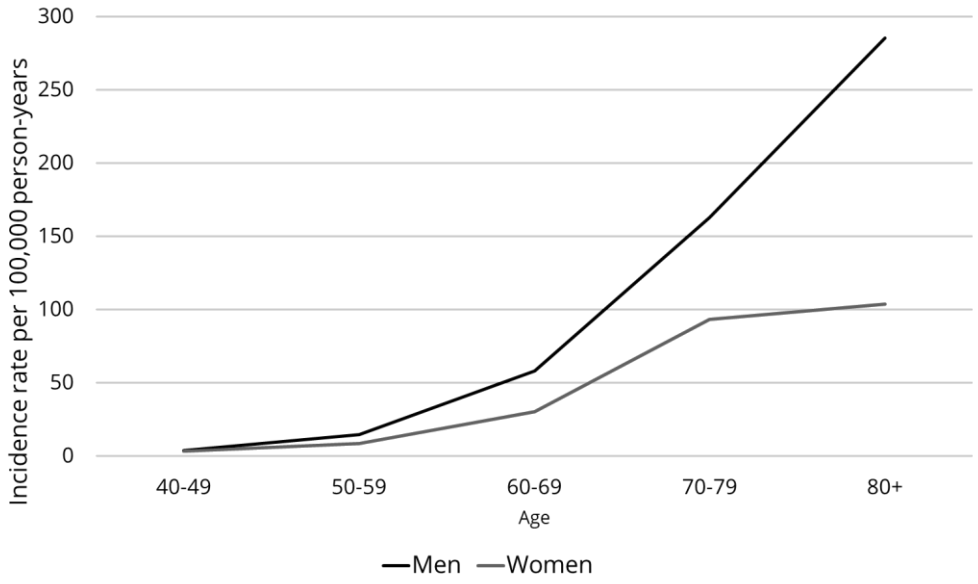


Figure 2. Incidence of Parkinson's disease in different age groups by sex. Data is derived from a meta-analysis by Hirsch et al, 2016.

Sex

Sex differences exist: PD is about twice as common in men compared to women (Cerri et al., 2019; Van Den Eeden et al., 2003). According to a meta-analysis, overall PD incidence rate in those 40 and older was 37.55 per 100,000 person-years in women and 61.21 in men (Hirsch et al., 2016). Clinical presentation and disease course can differ between sexes (Cerri et al., 2019). Motor symptoms can emerge later in women, but many non-motor symptoms can be more severe and more common among women. In addition, in men and women, the pathogenic mechanisms involved might be different. Hormonal differences, especially due to oestrogen, as well as genetic and molecular factors, contribute to sex differences (Vaidya et al., 2021).

Genetics

Genetic factors contribute to PD risk, and their prevalence can vary between different ethnic groups (Hernandez et al., 2016; Shu et al., 2019). Approximately 5-10% of PD may be monogenic, caused by mutations in a single gene (Jia et al., 2022). More than 20 genes causing monogenic forms of PD exist, and well-established genes have autosomal dominant forms of inheritance (such as *SNCA* and *LRRK2*) and recessive ones (such as *PRKN*, *PINK1* and *DJ-1*) (Blauwendraat et al., 2020; Klein and Westenberger, 2012). The first PD-related gene, synuclein alpha (*SNCA*), was identified in 1997 (Billingsley et al., 2018). Despite the importance of α-synuclein in PD pathogenesis, *SNCA* mutations causing monogenic PD are somewhat rare. Mutations in leucine-rich repeat kinase 2 (*LRRK2*) are the most common cause of familial PD (Hernandez et al., 2016). Worldwide, the common mutation Gly2019Ser in *LRRK2* was identified in 4% of persons with hereditary PD and 1% of persons with sporadic PD (Healy et al., 2008). Genetic risk factors are also associated with increased susceptibility to developing PD (Hernandez et al., 2016). Mutations in the gene that encodes glucocerebrosidase are the most common genetic risk factor known, and carriers can have about 5-fold increased PD risk (Sidransky et al., 2009).

Those with genetic causes tend to have earlier disease onset, especially for recessively inherited genes such as *PRKN* (<40 years) and, compared to idiopathic PD, progression rate might be faster or slower (Kasten et al., 2018; Wirdefeldt et al., 2011).

2.3.2 Modifiable risk factors

Environmental toxins

Several environmental, lifestyle, and dietary factors, as well as comorbid conditions and drugs, have been investigated as potential modifiable risk factors (Belvisi et al., 2020). Awareness that environmental toxins increase PD risk comes from the 1980s discovery that a metabolite of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a contaminant in synthetic heroin, causes parkinsonism symptoms indistinguishable from PD (Ascherio and Schwarzschild, 2016; Pang et al., 2019). The herbicide, paraquat, which has a structure similar to that of MPTP and causes oxidative stress, was also associated with increased PD risk (Tanner et al., 2011). A pesticide, rotenone, was linked to increased PD risk, probably via disrupting mitochondrial function. However, for these compounds, most PD cases lack exposure history; thus, other factors must also play a role (Pang et al., 2019).

Smoking

Smoking has been consistently associated with decreased PD risk in observational studies, but the reason cigarette smoking is a protective factor is debated (X. Li et al., 2015). Nicotine may influence dopaminergic activity by acting on nicotinic acetylcholine receptors although which cigarette-derived chemical explains the inverse association is unknown (Quik et al., 2012). On the other hand, the inverse association could be biased (Gallo et al., 2019). Reverse causality could be one explanation since responsiveness to nicotine during the prodromal stage may be reduced; thus, quitting smoking can be easier (Ritz et al., 2014). Another suggestion

is that persons with PD could be less likely to start smoking due to a low-risk-taking personality trait (Gallo et al., 2019; Kaasinen et al., 2001). However, when compared to never smokers, reduced PD risk has appeared in not only current smokers but those who had quit smoking up to 30 years before PD onset (Gallo et al., 2019). Passive smoking has also been associated with reduced PD risk (Searles Nielsen et al., 2012). A dose-response relationship has emerged and, for risk reduction, long-term smoking might be more important than smoking intensity (Chen et al., 2010). Another possibility is that smoking could merely delay PD onset. Heavy smokers may develop PD at older age (Kandinov et al., 2009), but contradictory findings exist (Gallo et al., 2019). Moreover, the association might be due selection bias if smokers die younger from non-PD causes (Hernán et al., 2002).

The global age-standardised prevalence of smoking has reduced in both men (27.5%) and women (37.7%) during 1990-2019 (GBD 2019 Tobacco Collaborators, 2021). Over the past few decades, smoking rates have declined also in Finland (Ruokolainen et al., 2019). If the inverse association between smoking and PD is truly causal, the declining trend of smoking could partly explain why PD incidence has been rising (Dorsey et al., 2018).

Comorbid conditions

Numerous comorbid conditions are associated with PD risk (Ascherio and Schwarzschild, 2016; Schrag et al., 2022). Different head injuries and traumatic brain injuries have been associated with higher risk of developing PD (Camacho-Soto et al., 2017; Gardner et al., 2015; Jafari et al., 2013). Traumatic brain injuries can cause deformation of brain tissue and disrupt normal function in the brain (Mckee and Daneshvar, 2015). One explanation for the increased PD risk is that brain injury can lead to dysfunction of the blood-brain barrier and induce neuroinflammation along with mitochondrial dysfunction (Jafari et al., 2013). Reverse causality might explain the results if a brain injury has occurred very close to PD diagnosis since, closer to motor symptom onset, persons might experience a fall-related brain injury (Camacho-Soto et al., 2017; Rugbjerg et al., 2008).

Several cardiovascular risk factors are connected to PD, but associations for many, such as type 2 diabetes, are controversial (Cheong et al., 2020; Potashkin et al., 2020). In a meta-analysis, cohort studies on diabetes and subsequent PD risk showed increased risk whereas case-control studies showed decreased PD risk (Noyce et al., 2012). Heterogeneity of methods and definitions of diabetes and PD might explain these conflicting findings. Many pathophysiological mechanisms in type 2 diabetes might contribute to PD development, but insulin resistance can play a key role (Fiory et al., 2019). Insulin acts on the dopaminergic system—for example, by modulating dopamine synthesis. Experimental evidence demonstrates that hyperglycaemia can induce nigrostriatal degeneration and neuroinflammation (Lv et al., 2022).

Other cardiovascular risk factors including hypertension and hypercholesterolemia have had divergent associations; increased risk (Schrag et al., 2022), decreased risk (Miyake et al., 2010), and no association have been reported (Savica et al., 2012). Although changes in glucose and lipid metabolism and inflammation connect cardiovascular risk factors and PD, evidence for these risk factors is not robust (Potashkin et al., 2020). Another controversial topic is the association of statins. In a meta-analysis including both case-control and cohort studies, compared to nonusers, statin users had 30% lower PD risk (Poly et al., 2017). Another meta-analysis examined the association between statin use and PD risk separately based on adjustment with either cholesterol or hyperlipidaemia or without adjustment (Bykov et al., 2017). Studies that did not adjust for cholesterol or hyperlipidaemia showed 25% risk reduction for PD; however, those studies that adjusted highlighted no significant association. Thus, the implied neuroprotective association between statins and PD risk could be confounded by indication.

2.3.3 Methodological challenges

The literature on risk factors is difficult to interpret since studies have heterogeneous findings and methodological differences. Observational studies are prone to different kinds of bias and confounding, which can result in over- or underestimation of risk. Measuring risk factors for a disease with a long latency period poses particular challenges (Bjornevik et al., 2020).

In PD risk factor studies, the exposure to a factor of interest should be evaluated during a period while it could influence PD pathogenesis. If the exposure is measured close to PD diagnosis, it might be irrelevant in terms of PD development. The association observed between a risk factor and PD may stem from functional, behavioural, and lifestyle changes resulting from early PD symptoms. For example, reduced physical activity closer to PD onset might seem to be a PD risk factor, but it could be a result of PD prodromal symptoms such as fatigue and pain (Chen, 2018; Sääksjärvi et al., 2014). Additionally, prodromal symptoms may reduce or increase drug prescription due to increased health care visits. This phenomenon, reverse causality or protopathic bias, may be minimized by applying a lag period between exposure and incident PD, i.e., excluding exposure within a certain period preceding the outcome in case-control studies (Tamim et al., 2007). Exposure may also delay or shorten the time to diagnose PD by causing symptoms that might imitate PD ones. Thus, exposure may spuriously seem like a risk factor. In cohort studies, if the outcome is measured soon after exposure, the association may be due to detection bias (Arfè and Corrao, 2015). In such cases, the initiation of a new drug may increase the probability of identifying PD due to persons' more regular use of health services.

Available data sources may place some limitations. Self-reported data on exposure, for example by way of questionnaires or interviews, can be prone to recall bias (Nielsen et al., 2008). As for PD, knowing exposure history 10-20 years before PD diagnosis would be preferable, and acquiring this knowledge via interviews may be unreliable. Using routinely collected health care data with long availability avoids this unreliability, but data

might still be missing, for example due to over-the-counter drugs, the use of which is often unrecorded in registers (Furu et al., 2010). Acknowledging all possible confounding factors might be impossible due to data limitations, measurement errors, or unknown factors, leading to residual confounding (Psaty et al., 1999; Schneeweiss, 2006). For example, information on smoking might be unrecorded in the register data, but it would be important to account for when studying PD risk factors.

A distinctive feature when drugs are studied as risk factors is the possibility of confounding by indication, which occurs when the underlying indication for drug use is also related to PD risk (Psaty et al., 1999). One option to account for confounding by indication is to restrict the study population with this disease. However, confounding may still exist if disease severity differs between groups being compared. Another possible means of reducing confounding by indication is to use an active comparator: the drug of interest is compared to a treatment with the same indication (Lund et al., 2015). This approach can be limited by two challenges: finding an appropriate active comparator and interpreting findings if the risk of an active comparator for PD is unknown (Yoshida et al., 2015).

2.4 DISEASE-MODIFYING ANTIRHEUMATIC DRUGS AND RISK OF PARKINSON'S DISEASE

2.4.1 Rheumatoid arthritis

RA is a chronic systemic autoimmune disease characterized by synovitis and formation of invasive synovial tissue (Smolen et al., 2018). These changes lead to joint damage by destructing cartilage and bone. Typically, small peripheral joints are initially affected symmetrically (Aletaha and Smolen, 2018). In addition to joints, RA may also manifest in other tissues—for example, in the lungs and heart (Smolen et al., 2018). A specific cause is unknown, but genetic risk factors play a role, and certain class II human leukocyte antigen regions are especially associated with RA risk. Risk is generally higher among women and smokers. RA has been divided into seropositive and seronegative, and autoantibodies may be present years before RA onset (Aletaha et al., 2010). Incidence and prevalence differ between countries and ethnicities, but they also depend on RA definition (Alamanos et al., 2006). In the Northern Savo population in Finland, the crude incidence of seropositive RA was 22.3/100,000 person-years in 2020 (Elfving et al., 2023).

RA classification criteria have changed in the most recent American College of Rheumatology/European League Against Rheumatism classification criteria released in 2010 (Aletaha et al., 2010). For example, the distinction between seropositive and seronegative RA is based on the presence of rheumatoid factor, anti-citrullinated protein antibodies (ACPAs), or both in the serum. The role of ACPAs was discovered in the 1990s and was missing from American College of Rheumatology 1987 classification criteria (Aletaha et al., 2010; Arnett et al., 1988). Among attempts to identify RA at an earlier stage, an example is that erosions, which are related to more advanced disease, were not included in the 2010 criteria.

Seropositive and seronegative RA are different disease entities with aetiological and clinical differences (De Stefano et al., 2023). Seronegative

RA has a heterogeneous nature (Paalanen et al., 2021). During follow-up, the initial diagnosis of seronegative RA may change into other diagnoses. Seronegative RA has been reclassified into seropositive or into other joint diseases such as spondyloarthritis, as in a Finnish study that followed incident seronegative RA patients for 10 years (Paalanen et al., 2019).

2.4.2 Rheumatoid arthritis and Parkinson's disease

RA definitions in epidemiological studies on the relationship between RA and PD risk have been divergent (Table 3). Serology impact on PD risk has been largely unexplored. Only one, a cohort study by Kang et al. (2023) differentiated RA based on serology. Due to potential prognostic differences based on serology and possible misclassification of seronegative RA (De Stefano et al., 2023; Paalanen et al., 2019), serotypic differentiation would be a matter of interest. Keeping in mind that RA is a heterogeneous disorder in itself and classification criteria have been updated (Aletaha et al., 2010), findings from previous studies may not be directly comparable due to population differences.

In most epidemiological studies, RA has been associated with decreased PD risk (Table 3). In a Danish case-control study, persons diagnosed with RA at least five years before PD, had 30% decreased PD risk (Rugbjerg et al., 2009). Decreased PD risk was observed also with a longer lag period of 10-14 years (odds ratio (OR) 0.5; 95% confidence interval (CI) 0.3-0.9). Risk reduction with lag periods of 5-9 or ≥15 years was non-significant. Adjustment with chronic obstructive pulmonary disease (COPD) as proxy for smoking did not change the results.

A Swedish nested case-control study also applied different lag periods between RA and subsequent PD diagnosis (Bacelis et al., 2021). Inverse association was constantly observed regardless of lag length, with ORs ranging between 0.54 and 0.50 with lag periods from 1 to 8 years. However, the study population and design differ compared to those in Rugbjerg et al. (2009). Bacelis et al. used a dataset of persons with diabetes or celiac diseases and their first-degree relatives unlike Rugbjerg et al., who used nationwide population-based data from Denmark. Bacelis et al. had

two different ways of defining PD. In the conservative method, PD diagnosis had to be the main diagnosis in the outpatient register. In the inclusive method, all persons with PD as main or secondary diagnosis recorded in outpatient or inpatient registers were included. Compared to the inclusive method, the conservative one resulted in fewer PD cases, and persons were younger at their first PD diagnosis. Although inverse associations were observed with both PD definitions, the conservative definition yielded lower ORs than the inclusive one did. For example, with a 5-year lag, the OR for the conservative method was 0.47 and for the inclusive one 0.65. Bacelis et al. did not adjust analyses with any potential confounders, but they matched PD cases and controls by birth year, sex, birth location, follow-up time, and relative type.

In a Taiwanese cohort study, compared to persons without RA, persons with RA had 35% decreased risk of PD development (hazard ratio (HR) 0.65; 95% CI 0.58-0.73) (Sung et al., 2016). Incidence rates (IRs) per 1000 person-years were 1.64 for RA and 2.67 for comparison persons. Analyses were stratified by follow-up period ≤4, 5-8, 9-12, and >12 years; with longer follow-up periods, stronger inverse associations emerged (HRs ranging 0.65-0.22). However, most PD cases were already identified within ≤8 years after follow-up start. Persons in the study cohort were relatively young in terms of PD development, with the approximate average age at RA diagnosis being 54. However, in age-stratified analyses, decreased risk was evident also among those aged ≥65 at RA diagnosis (HR 0.62; 95% CI 0.54-0.72).

On the contrary, in another Taiwanese cohort study, persons with RA had a 14% increase in relative PD risk compared to persons without autoimmune rheumatic diseases, which included nine diseases such as systemic lupus erythematosus, systemic sclerosis, and Sjögren's syndrome (HR 1.14; 95% CI 1.03-1.28) (Chang et al., 2018). The IR per 10,000 person-years was 30.78 for RA and 25.79 for comparison persons. The association remained similar irrespective of age stratification (<65, ≥65 at RA diagnosis).

No clear explanations exist for contradictory findings on the RA-PD relationship from these two Taiwanese cohort studies (Chang et al., 2018;

Sung et al., 2016). Increased PD risk for RA in Chang et al. (2018) could be due to detection bias since PD may have been diagnosed directly after RA. However, reduced risk was observed in Sung et al. (2016), which had a very similar follow-up period for PD onset (Table 3). Chang et al. did not stratify analyses by follow-up period; thus, whether HRs would have declined among those with longer follow-up is unknown. The discrepancy is not due to differences in applied diagnosis codes to define RA and PD; the same codes were applied in both studies (Table 3). However, in Chang et al., PD had to be diagnosed by a neurologist, and only an inpatient setting or ≥3 visits in an outpatient setting were required. One possible explanation is the different comparison group. While, in Sung et al., the comparison group consisted of persons without RA, Chang et al. also excluded from the comparison group persons with eight other autoimmune rheumatic diseases. Chang et al. restricted the study population to persons aged ≥45 while Sung et al. had no restrictions for age, and 39% of the study population were ≤49. In younger populations, baseline PD risk is presumably lower, which may have affected their results. Neither study had information on disease severity and smoking status; this lack may have led to residual confounding.

A Korean cohort study examined PD risk based on RA presence and its serologic status, with a 1-year lag between RA and PD (Kang et al., 2023). Interestingly, compared to persons without RA, persons with RA had a 1.74-fold increased PD risk (HR 1.74; 95% CI 1.52-1.99). After stratifying by serology, they found seropositive RA was associated with increased PD risk regardless of the covariates used. However, seronegative RA had no association with PD risk after adjusting for age, sex, smoking, body mass index, diabetes, hypertension, hyperlipidaemia, chronic kidney disease, myocardial infarction, stroke, and depression. Compared to those with seronegative disease, persons with seropositive RA exhibited higher PD risk (HR 1.61; 95% CI 1.20-2.16). Similar results for all these analyses were observed with longer lag periods (2, 3, and 5 years).

Furthermore, one study detected no association between RA and PD (Li et al., 2012). It examined PD incidence for 33 different autoimmune and related disorders such as RA, Graves' disease, and ulcerative colitis, and

compared it to that in a reference group without these disorders. The standardized incidence ratio (SIR) for PD in persons with RA compared to the reference group without multiple different autoimmune disorders was 1.07 (95% CI 0.89-1.26). The association remained nonsignificant when stratified by follow-up time (≥1 or ≥5 years) after hospitalization for RA. However, an inverse association emerged in the oldest age group of ≥80-year-olds among those with follow-up time ≥1 year (SIR 0.64; 95% CI 0.42-0.94).

The RA-PD relationship has also been assessed with Mendelian randomization (MR) analysis, a genetic epidemiological method that uses genetic variants as instrumental variables for risk factors (Davies et al., 2018; Li et al., 2021). Li et al. (2021) used single nucleotide polymorphisms (SNPs), which were obtained from genome-wide association studies of European ancestry on RA and PD, as instrumental variables and conducted a two-sample MR analysis. Their findings support the view that RA is associated with reduced PD risk. One standard deviation (SD) increase in RA risk resulted in a 10% decrease in PD risk (OR 0.90; 95% CI 0.87-0.94). Another MR study also reported a decreased PD risk for genetically predicted RA (OR 0.91, p=0.007) (Guo et al., 2022).

The association between RA and PD risk remains inconclusive. Some theoretical explanations exist for the direction of the association. Chronic inflammation and inflammatory mediators, including tumour necrosis factor (TNF) and interleukin-6 (IL-6), secreted in RA could launch neurodegeneration in PD and explain increased PD risk (Chang et al., 2018; Kang et al., 2023). A co-pathogenetic link between these two diseases was already suggested earlier (Kogure et al., 2008). Additionally, evidence exists of overlap between genetic risk factors for PD and RA (Witoelar et al., 2017). This hypothesis is contradicted by many studies showing reduced PD risk among persons with RA. The association may be confounded by lifestyle factors and gender differences. For example, smoking increases RA risk (Sugiyama et al., 2010), while reducing PD risk (Gallo et al., 2019). Unlike PD (Cerri et al., 2019), RA is more common in women (Favalli et al., 2019). Furthermore, drugs used to treat RA could influence PD risk and mediate risk reduction (Gonzalez-Latapi and Marras, 2022).

Table 3. Summary of studies on the relationship between RA and PD risk.

Reference, country, study type	**Population, sample size, mean age, sex**	**RA definition, identification period**	**PD definition, identification period**	**Relative risk (95% CIs): RA yes vs no**
(Kang et al., 2023), Korea cohort	Persons with RA (N=54,680) and 1:5 matched comparison persons without RA (N=273,400) aged ≥40. 58.6, 74.9% women	Seropositive: ICD-10 M05 Seronegative: ICD-10 M06 (except M06.1, M06.4) Prescription of any DMARD for ≥180 days. 2010-2017	ICD-10: G20 1 year after RA onset until 2019 Median follow-up 4.3 years	A 1-year lag between RA and subsequent PD Seropositive: HR 1.95 (1.68-2.26) Seronegative: HR 1.20 (0.91-1.57)
(Bacelis et al., 2021), Sweden nested case-control	3.6 million inhabitants of Sweden that had diabetes or celiac disease or their first-degree relatives as source population. Cases with PD (N= 4,738) and matched controls (N=47,269) Median age in persons with PD: 69, N/A	ICD-10: M05, M06 1997-2017	ICD-7: 350; ICD-8: 342; ICD-9: 332A; ICD-10: G20 Conservative definition: PD as the main diagnosis in outpatient register. Those excluded were with syphilis, schizophrenia, secondary parkinsonism, other extrapyramidal movement disorders, or other degenerative diseases of the basal ganglia. 1964-2017	A 1-year lag between any RA and subsequent PD OR 0.54 (0.37-0.76)

Table 3 (continued)

Reference, country, study type	Population, sample size, mean age, sex	RA definition, identification period	PD definition, identification period	Relative risk (95% CIs): RA yes vs no
(Chang et al., 2018) Taiwan cohort	34,606 persons aged ≥45 with ARD, of which RA N=19,542. Matched comparison persons without ARD (N=138,424). 59.8, 77.3% women (total study population)	ICD-9 CM: 714 2001-2012	ICD-9 CM: 332 inpatient or ≥3 outpatient visits 2002-2012 Mean follow-up (years) in persons with ARD 6.0, comparison persons 6.4	Any RA HR 1.14 (1.03-1.28)
(Sung et al., 2016), Taiwan cohort	Persons with RA (N=33,221) and 4 matched comparison persons without RA (N=132,884) 53.9 (persons with RA), 53.4 (comparison persons), 77.6% women	ICD-9 CM: 714 1998-2010	ICD-9 CM: 332 1998-2011 Mean follow-up (years) in persons with RA 6.6, comparison persons 6.7	Any RA HR 0.65 (0.58-0.73)

Table 3 (continued)

Reference, country, study type	Population, sample size, mean age, sex	RA definition, identification period	PD definition, identification period	Relative risk (95% CIs): RA yes vs no
(Li et al., 2012), Sweden cohort	310,522 persons with autoimmune disorders, of which persons with RA N=52,994. Comparison group persons were without history of autoimmune disorders. N/A, 54.8% women (persons with autoimmune disease and PD)	ICD-7: 722 (excluded 722.1); ICD-8: 712.1, 712.3; ICD-9: 714 (excluded 714E, 714X); ICD-10: M05, M06, M08.0, M08.2 1964-2007	ICD-7: 350; ICD-8: 342.0; ICD-9: 332; ICD-10: G20 and G21 1964-2007 Follow-up 1-44 years	Any RA SIR 1.07 (0.89-1.26)
(Rugbjerg et al., 2009), Denmark case-control	Cases with PD (N=13,695) and up to 5 matched controls (N=68,445) 73.0, 45.8% women	ICD-8: 712.09-712.39, 712.59 Between 1977 and 5 years before PD diagnosis/index date	ICD-8: 342, ICD-10: G20. Persons aged <35 excluded 1986-2006	A 5-year lag between any RA and subsequent PD OR 0.7 (0.5-0.9)

Abbreviations: ARD=autoimmune rheumatic disease; CM=clinical modification; DMARD=disease-modifying antirheumatic drug; HR=hazard ratio; ICD=international classification of diseases; N/A=not available; OR=odds ratio; PD=Parkinson's disease; RA=rheumatoid arthritis; SIR=standardized incidence ratio

2.4.3 Disease-modifying antirheumatic drugs and Parkinson's disease

DMARDs interfere with inflammation and, by definition, inhibit joint damage progression (Aletaha and Smolen, 2018). The therapeutic goal in RA is remission or, if remission cannot be achieved, low disease activity. DMARDs can be sub-grouped into synthetic and biologic agents. Synthetic DMARDs have various molecular targets and include the first-line therapy methotrexate, as well as hydroxychloroquine and sulfasalazine. The combination of these three DMARDs forms the so-called triple therapy, which has proved effective in early RA (Möttönen et al., 1999). Targeted synthetic DMARDs are newer types of agents and include Janus Kinase inhibitors such as tofacitinib and baricitinib (Aletaha and Smolen, 2018). Biologic DMARDs have specific targets in the immune system pathway. Adalimumab, etanercept, and certolizumab pegol target TNF-α; tocilizumab targets IL-6. Rituximab binds the B-cell-specific antigen CD20, and abatacept targets T-cell co-stimulation. Biologic DMARDs are usually used in combination with methotrexate and only if adequate treatment response is not achieved with two or more synthetic DMARDs or if poor prognostic factors such as early joint damage are present (Smolen et al., 2020). Corticosteroids can be used adjunctive to DMARDs, but side effects preclude their long-term use.

Drugs used in RA treatment could reduce PD risk (Gonzalez-Latapi and Marras, 2022), but studies on the association between different DMARDs and PD risk are scarce. A Taiwanese cohort study investigated the association between RA and PD risk and observed whether DMARDs influence this association (Table 3) (Sung et al., 2016). Compared to persons without RA, both persons with RA who were DMARD users (HR 0.66; 95% CI 0.57-0.77) and nonusers (HR 0.64; 95% CI 0.55-0.74) had reduced PD risk. Persons with RA who used biologic DMARDs had even lower PD risk (HR 0.57; 95% CI 0.41-0.79). Associations were unreported for individual DMARDs. A Korean cohort study that observed the relationship between RA and PD risk (Table 3) reported the opposite; nonusers of biologic DMARDs with RA had an increased PD risk, compared to comparison persons without RA (HR 1.78; 95% CI 1.54-2.04) (Kang et al.,

2023). Biologic DMARDs were not associated with PD risk (HR 1.16; 95% CI 0.65-2.05), but the statistical power of this analysis was limited.

A population-based case-control US study investigated the relationship between different DMARDs and immunosuppressants and PD risk (Racette et al., 2018). They classified drugs into calcineurin inhibitors (ciclosporin, tacrolimus), inosine monophosphate dehydrogenase (IMDH) inhibitors (azathioprine, leflunomide and mycophenolate), dihydrofolate reductase inhibitors (methotrexate), biologic DMARDs (abatacept, adalimumab, anakinra, certolizumab and etanercept), corticosteroids, and a group with miscellaneous drugs, including hydroxychloroquine and sulfasalazine. Drug use was identified during 2008-2009, and cases were required to have PD diagnosis in 2009 without any codes for PD five years prior to it. Their statistical model was adjusted for age, sex, race/ethnicity, smoking, and use of medical care. IMDH inhibitors on a class level were associated with reduced PD risk, with or without a 1-year lag. However, with a 1-year lag, associations for individual drugs within IMDH inhibitors were no longer significant; the small number of users may have led to lack of power. Methotrexate had an inverse association with PD risk (OR 0.84; 95% CI 0.74-0.95) as did hydroxychloroquine (OR 0.77; 95% CI 0.65-0.90); however, for both drugs, with a 1-year lag, the association attenuated. Neither sulfasalazine nor biologic DMARDs were associated with PD risk. Corticosteroid use was associated with reduced PD risk, with a 1-year lag (OR 0.81) and without it (OR 0.80). That study was limited by the short exposure assessment window of a maximum of 2 years, which may have caused drug exposure misclassification and partially explains the small number of users for some drugs. The lag period of 1 year is short in terms of PD development.

A recent US study attempted to identify drugs associated with lower PD risk, by using the same Medicare data as Racette et al. (2018) did, with incident PD diagnosed in 2009 as the outcome (Song et al., 2023). Drug exposure was determined during 2006-2007 with at least a 1-year lag, and results were adjusted for age, sex, race/ethnicity, use of medical care, as well as lung cancer and COPD as indicators of smoking. Compared to nonuse, chloroquine/hydroxychloroquine use was associated with lower

PD risk (OR 0.84; 95% CI 0.73-0.96), and a borderline inverse association was observed for methotrexate (OR 0.90; 95% CI 0.80-1.01).

SNPs from genome-wide association studies of European descent on RA and PD were used by a two-step MR study as instrumental variables (Guo et al., 2022). They evaluated whether immunosuppressants, in addition to corticosteroids and nonsteroidal anti-inflammatory drugs (NSAIDs), mediate the RA-PD association. Immunosuppressants consisted of methotrexate, azathioprine, mycophenolate, leflunomide, adalimumab, cyclosporine, tacrolimus, and sirolimus. These authors reported that persons with RA had an increased use of immunosuppressants, which decreased PD risk (OR 0.82, p=0.03), with similar findings reported for corticosteroids (OR 0.86, p=0.03).

Synthetic and biologic DMARDs might reduce PD risk (Guo et al., 2022; Racette et al., 2018; Song et al., 2023; Sung et al., 2016). Since RA is associated with PD, potential confounding by indication can be reduced by comparing the association between DMARDs and PD risk among persons with RA. Indication-restricted studies assessing PD risk for specific DMARDs among persons with RA are, however, missing. Overall, drug-specific information on PD risk is insufficient. DMARDs are a group of drugs, each of which has a unique mechanism of action explaining their anti-inflammatory and immunosuppressive properties. Information on whether only certain drugs within DMARDs are responsible for potential risk reduction could give more insight into underlying PD disease processes.

2.5 B2AR AGONISTS AND RISK OF PARKINSON'S DISEASE

2.5.1 Asthma and chronic obstructive pulmonary disease

Asthma and COPD may be potential risk factors for PD (Cheng et al., 2015; C.-H. Li et al., 2015). Both are heterogeneous conditions that cause airflow obstruction and reduced lung function; however, pathogenesis and disease progression differ between asthma and COPD (Yayan and Rasche, 2016). Life expectancy in persons with COPD is shortened due to increased morbidity and mortality while persons with asthma can live to old age with good asthma management (GOLD, 2023; Haahtela, 2006; Yayan and Rasche, 2016).

Asthma may begin at any age from childhood to adulthood (Papi et al., 2018). Asthma is associated with airway hyperresponsiveness, defined by an excessive response to a stimulus resulting in narrowing of the airways (Chapman and Irvin, 2015). Typical symptoms are wheezing, chest tightness, shortness of breath, and cough (Papi et al., 2018). Asthma phenotypes are many and include childhood-onset allergic, non-allergic, and occupational asthma. The most important subtype according to underlying inflammatory mechanisms is eosinophilic asthma, which can be either allergic or non-allergic. Other subtypes include neutrophilic, paucigranulocytic, and mixed granulocytic asthma. Airflow obstruction in asthma is often variable and reversible. However, airway remodelling can cause structural changes, including epithelial cell damage, increased airway smooth muscle mass, fibroblast activation, and increased vascularity of the airways (Hough et al., 2020). These changes influence the degree of airflow obstruction, which may become persistent.

COPD prevalence is higher among smokers than in non-smokers and is often diagnosed later in life (GOLD, 2023). Smoking is the greatest COPD risk factor, but other noxious particles such as air pollutants also increase risk. Characteristic features are chronic respiratory symptoms including sputum production, cough, and shortness of breath. Airflow obstruction is persistent and often progressive. These symptoms are related to chronic bronchitis, emphysema, and narrowing of the small airways. Chronic

inflammation contributes to structural changes in the airways, lung parenchyma, and pulmonary vasculature. Persons with COPD may develop abnormal pulmonary gas exchange, which can result in hypoxaemia i.e., low blood oxygen (GOLD, 2023; Sarkar et al., 2017). Pulmonary hypertension may develop in advanced disease (GOLD, 2023). In addition to inflammation in the lungs, systemic inflammation may occur, and it can be related to comorbidities, such as cardiovascular diseases, which often coexist with COPD. Asthma and COPD features may overlap, and cause worse symptoms than with asthma or COPD alone (Nielsen et al., 2015).

2.5.2 Asthma/chronic obstructive pulmonary disease and Parkinson's disease

Previous studies on the relationship between asthma/COPD and PD risk are limited. In a Taiwanese cohort study, persons with asthma (n=10,455) had a 3-fold increased PD risk (HR 3.10; 95% CI 2.20-4.36) in comparison to persons without asthma (n=41,820), during a maximum follow-up of 13 years (Cheng et al., 2015). The association remained after exclusion of observations in the first year or the first three years after cohort entry although estimates were diluted after excluding PD diagnosis during the first year (HR 2.90; 95% CI 2.04-4.13) and the first three years (HR 2.46; 95% CI 1.64-3.69). This dilution might reflect detection bias in the main results, meaning that asthma diagnosis may result in earlier PD identification. Inhaled β2-adrenoceptor (β2AR) agonists were included as a covariate; when use was compared to nonuse, their use was not associated with the risk of developing PD among persons with asthma and their comparison persons without asthma. A case-control study of 196 case-control pairs based in Olmsted County in Minnesota, USA, observed no association between asthma and PD risk (OR 1.8; 95% CI 0.8-3.9) (Bower et al., 2006). However, the study population was small; as 19 cases and 11 controls had asthma, power to detect a significant association was limited. In a Taiwanese cohort study with a maximum follow-up of 13 years, compared with persons without COPD (n=41,147), persons with COPD (n=20,728) had a 1.37-fold increased PD risk (95% CI 1.25-1.50) (C.-H. Li et al., 2015). In that

study, PD may have been diagnosed directly subsequently to COPD, and detection bias cannot be ruled out. None of the said three studies on asthma or COPD accounted for smoking in their analyses (Bower et al., 2006; Cheng et al., 2015; C.-H. Li et al., 2015).

On the contrary, in a population-based case-control study that assessed the relationship between β2AR agonists and PD, both asthma and COPD were associated with decreased PD risk when adjusted for smoking, number of unique diagnosis codes, age, sex, and race (Searles Nielsen et al., 2018). Asthma and COPD were defined for the purpose of adjustment in the analyses but were also examined as separate factors. The presence of asthma or COPD was measured during 6 years prior to PD diagnosis. In another case-control study with a similar focus on the relationship between β2AR agonists and PD, COPD diagnosis was associated with decreased PD risk (Hopfner et al., 2019).

The biological link between these pulmonary diseases and PD is unclear. Inflammatory processes may contribute to PD development (Cheng et al., 2015; C.-H. Li et al., 2015). Pro-inflammatory cytokines secreted in asthma, for example IL-6 and TNF, are linked to neurodegenerative processes in PD (Barnes, 2008; Tan et al., 2020). Systemic inflammation particularly in COPD may also contribute to PD risk (Wouters et al., 2009). As pulmonary function and gas exchange decline in COPD, the risk of both hypoxaemia (low blood oxygen) and hypoxia (low oxygen levels in tissues) increases (Kent et al., 2011; Sarkar et al., 2017). A transcription factor, hypoxia-inducible factor-1 (HIF-1), is an important regulator of oxygen homeostasis and enables adaptation to hypoxia, for example by inducing erythropoietin expression (Lestón Pinilla et al., 2021). HIF-1 expression is elevated in persons with COPD (Rong et al., 2018). HIF-1 signalling has been recently linked to PD-related genes, and hypoxia can induce, for example, oxidative stress, which is implicated in PD pathophysiology (Lestón Pinilla et al., 2021). Because the brain consumes much oxygen, it is vulnerable to hypoxia, which could explain the relationship between obstructive pulmonary diseases and PD.

2.5.3 β2AR agonists and Parkinson's disease among persons with asthma/chronic obstructive pulmonary disease

β2ARs are primarily present in airway smooth muscles although they are also expressed, for example, in cardiac muscles and in white blood cells, including eosinophils and neutrophils (Abosamak and Shahin, 2023). Inhaled β2AR agonists relax airway smooth muscle, and they are commonly used bronchodilators in both asthma and COPD (GINA, 2022; GOLD, 2023). Short-acting β2AR agonists such as salbutamol and terbutaline are hydrophilic, can access the receptor directly from the extracellular compartment, and have rapid onset of action (Johnson, 2006). However, their duration of action is short (4-6 hours). Long-acting β2AR agonists such as salmeterol and formoterol are more lipophilic and are absorbed into the cell membrane, from where they slowly access the active β2AR site. Their duration of action generally ranges between 12-24 hours (Fuso et al., 2013), with those with a 24-hour duration classified as ultra-long-acting; examples of this class are vilanterol, indacaterol, and olodaterol (Burkes and Panos, 2020).

An experimental study found that β2ARs regulate *SNCA* in a bidirectional manner; agonists such as clenbuterol reduced gene expression while a nonselective antagonist, propranolol, increased it (Mittal et al., 2017). As α-synuclein is an important factor in PD pathogenesis, its downregulation could be beneficial. Additionally, β2AR agonists may have neuroprotective and anti-inflammatory effects (Peterson et al., 2014). Since both asthma and COPD are linked with PD development, (Cheng et al., 2015; C.-H. Li et al., 2015), confounding by indication should be acknowledged. Regarding β2AR agonist-PD risk association in a population restricted to persons with asthma/COPD, epidemiological studies are scarce (Table 4).

In a nested case-control study of persons with COPD, compared to nonuse, regular dispensing of short- or long-acting β2AR agonists at least once in every six months for two years was not associated with reduced PD risk (Chen et al., 2020). The exposure assessment period of two years was followed by a 2-year lag period prior to PD. No association was observed in sensitivity analyses with a 3-year lag period or in analyses that controlled

for competing risk of death by counting deaths as PD. Study limitations included a short exposure assessment period close to PD diagnosis despite the effort of categorizing use into irregular and regular (Table 4). Data on smoking was unavailable; however, if it is assumed that smoking was relatively evenly distributed in the population with COPD and was no longer a confounder, β2AR agonists were not associated with PD risk among persons with COPD.

A nested case-control study within a cohort of persons with asthma, COPD, or both, reported a 10% decreased PD risk per additional month of exposure to short-acting β2AR agonists (OR 0.90; 95% CI 0.86-0.96) (Marras et al., 2020). Those authors provided no risk estimates for long-acting β2AR agonists but stated that no association emerged. Study participants had prevalent asthma, COPD, or both, and had a one-year washout period, after which drug use was assessed as days supplied until incident PD. This washout period was not specific to β2AR agonists but excluded persons if they had used β2AR agonists, anticholinergics, or inhaled corticosteroids. Mean exposure duration for short-acting β2AR agonists for both controls (7.66; SD ±16.15) and PD cases (6.96; SD ±14.47) was roughly seven months; considerable variation in individual exposure duration was indicated by the large standard deviation. Therefore, the adequate duration of use for lower PD risk is difficult to estimate.

In a cohort restricted to persons with asthma/COPD (including bronchiectasis), each additional 30-day β2AR agonist claim per year was weakly associated with lower PD risk (OR 0.986; 95% CI 0.977-0.995) (Nadeem et al., 2022). Their analysis was adjusted for demographics, comorbidities, asthma and COPD severity, other drug use, and history of smoking based on smoking cessation claims from Medicare. β2AR agonist use duration is unclear, but users had, on average, four 30-day claims per year. In subgroup analysis by pulmonary disease type, β2AR agonist users had decreased PD risk only in persons with only COPD, when compared to the group with only asthma diagnosis. PD incidence during the four-year follow-up did not differ between β2AR agonist users (1.86%) and nonusers (1.88%), (p=0.70).

In conclusion, between indication-restricted studies on the relationship between β2AR agonists and PD among persons with asthma/COPD, direct comparison is challenging (Table 4). Exact definitions for β2AR agonists are unreported, and which individual drugs are included in short- or long-acting β2AR agonists remain unclear. Exposure assessment periods and follow-up times for PD onset differ. PD definition differs between studies, especially for exclusion criteria, and may affect associations observed as PD misdiagnosis is relatively common (Rizzo et al., 2016) (Table 5). Studies vary in the definition of asthma and COPD, further complicating comparison (Table 5).

Table 4. Summary of studies restricted to asthma/COPD and investigating the association between β2AR agonists and PD risk.

Reference, country, study type	**Population, data collection period**	**Exposure definition for β2AR agonist use, lag period, follow-up duration**	**N, mean age, sex**	**Odds ratio (95% CIs)**
(Nadeem et al., 2022), USA, cohort	Persons >65 years with asthma, COPD, and/or bronchiectasis diagnosis by 2007 without PD diagnosis prior to 2010. Grouped into β2AR users and nonusers. 2007-2014	Number of 30-day claims for β2AR agonists during 2007-2010 Followed for PD cases during 2011-2014: outcome variable 4-year PD incidence	Users of β2AR agonists: 126,882 Nonusers: 109,319 77.1, 32% men	Number of 30-day β2AR agonist claims: 0.986 (0.977-0.995)
(Chen et al., 2020), Canada, nested case-control	COPD cohort of persons ≥40 years. Cases with incident PD and up to 5 matched controls. 1995-2015	Short- and/or long-acting β2AR agonist use during 2 years: Regular use: ≥1 dispensation in every 6 months, Irregular use: ≥1 dispensation overall, but with at least 6 months of no use in 2 years 2-year lag At least 4-year follow-up	PD cases: 732 controls: 3,660 70.7, 63% men	Regular use vs nonuse: 1.14 (0.93-1.40) Irregular use vs nonuse: 1.15 (0.92-1.45)

Table 4 (continued)

Reference, country, study type	**Population, data collection period**	**Exposure definition for β2AR agonist use, lag period, follow-up duration**	**N, mean age, sex**	**Odds ratio (95% CIs)**
(Marras et al., 2020), Canada, nested case-control	Cohort of persons >65 years with asthma, COPD, or both, who newly started with β2AR agonists, anticholinergics, or inhaled corticosteroids. Cases with incident PD and 1:5 matched controls. 1997-2017	Short-acting β2AR agonists as months exposed Median follow-up for incident PD 60 months Mean exposure time as of the index date in months ± SD for short-acting β2AR agonists: controls 7.66 ± 16.15, PD cases 6.96 ± 14.47	PD cases: 3,568 controls: 17,822, 79.4, 62% men	Additional month of exposure to short-acting β2AR agonists: 0.90 (0.86-0.96)

Abbreviations: CI=confidence interval; COPD=chronic obstructive pulmonary disease; PD=Parkinson's disease; SD=standard deviation; β2AR=β2-adrenoceptor

Table 5. Definition of asthma/COPD and PD in indication-restricted studies on the relationship between β2AR agonists and PD risk.

Reference, country, database	**Asthma/COPD definition**	**PD definition**
(Nadeem et al., 2022), USA Medicare	Asthma: ICD-9 493.0–493.2, 493.8–493.9 COPD: ICD-9 490–492, 496 (including bronchiectasis ICD-9 494.0)	ICD-9 332.0. Those with essential tremor ICD-9 333.1 were excluded.
(Chen et al., 2020), Canada British Columbia health administrative databases	COPD: One or more hospitalizations or two or more outpatient physician visits during any 12-month rolling period, with COPD being the principal diagnosis: ICD-9 491, 492, 493.2, 496; ICD-10 J41, J43, J44	At least one outpatient visit or hospitalization for PD with ICD-9 332 or ICD-10 G20. These persons must have filled also ≥1 levodopa prescriptions within 90 days after first PD diagnosis. Persons with secondary parkinsonism, other degenerative diseases of the basal ganglia, and tremor were excluded (ICD-9 332.1, 333.0, 333.1; ICD-10 G21, G23.9, R25)
(Marras et al., 2020), Canada The Canadian Institute for Health Information Discharge Abstract Database, The Ontario Health Insurance Plan physician billing database	Asthma: At least one hospitalization or two outpatient visits with an asthma diagnosis: Ontario Health Insurance Plan codes 493 ICD-10 J45 COPD: At least one hospitalization, or one outpatient visit with a COPD diagnosis: Ontario Health Insurance Plan codes 491, 492, 496 ICD-10 J41, J43, J44	ICD-9 332 or ICD-10 G20 with one antiparkinsonian drug (levodopa, MAO-B inhibitor, dopamine agonists, or COMT inhibitor) prescriptions within 6 months of each other

Abbreviations: COMT=catechol-O-methyltransferase; COPD=chronic obstructive pulmonary disease; ICD=international classification of diseases; MAO=monoamine oxidase; PD=Parkinson's disease; β2AR=β2-adrenoceptor

2.5.4 β2AR agonists and Parkinson's disease among the general population

Initial interest in β2AR agonists stemmed from a Norwegian cohort study, in which salbutamol use was associated with reduced PD risk when compared to nonusers in age-, sex-, and level of education-adjusted analysis (rate ratio (RR) 0.66; 95% CI 0.58-0.76) (Mittal et al., 2017) (Table 6). On the contrary, in a case-control US study, salbutamol was associated with increased PD risk when adjusted for age, sex, and race (Searles Nielsen et al., 2018). The direction of association may be explained by detection bias since, interestingly, after researchers adjusted further with the number of unique diagnosis codes as a marker of use of care, the association was inverse also in the US study. Further adjustment with smoking resulted in a null association, implying that smoking plays a role as a confounder.

Risk estimates have been reported for some individual β2AR agonists in addition to salbutamol. In an Israeli study, salbutamol as well as formoterol and vilanterol were associated with reduced PD risk (ORs ranging 0.40-0.89) (Gronich et al., 2018). In a Danish case-control study, among individual drugs, compared to nonuse, salmeterol was the only one associated with statistically significant decreased PD risk (OR 0.54) (Hopfner et al., 2019).

Some studies have assessed dose-response relationship with PD risk but with divergent findings. Two studies calculated cumulative defined daily doses (DDDs) for salbutamol, using the following categorization: <60, 60-180, >180 DDDs (Mittal et al., 2017; Searles Nielsen et al., 2018). Mittal et al. (2017) compared use to nonuse and highlighted dose-dependent lower PD risk. Searles Nielsen et al. (2018) compared salbutamol use to the lowest exposure category; despite stratifying by smoking history, no dose-response association emerged among users. An Israeli nested case-control study conducted a dose-response analysis by comparing average daily dose quartiles of salbutamol to nonuse; risk was reduced except for the highest quartile (Gronich et al., 2018).

Some studies have analysed whether the association between β2AR agonists and PD risk is influenced by their duration of action. In a recent cohort study, short- or long-acting β2AR agonists were not associated with PD incidence (Liu et al., 2023), but contradictory findings exist. A nested case-control UK study observed that, compared to nonuse, the use of short-acting β2AR agonists was associated with reduced PD risk but long-acting ones were not (Giorgianni et al., 2020). In Gronich et al. (2018), compared to nonusers, users of short-, long- and ultra-long-acting β2AR agonists had reduced PD risk. The strongest risk estimates were for ultra-long-acting β2AR agonists, suggesting stronger risk reduction with longer duration of action (Table 6). Similar findings emerged in a Norwegian cohort study by Tuominen et al. (2023). Smoking may confound the association since ultra-long-acting β2AR agonists are often used in COPD (Burkes and Panos, 2020). In Tuominen et al. (2023), after excluding persons with COPD, short-, long-, or ultra-long-acting β2AR agonists were no longer associated with PD risk.

Two recent cohort studies also conducted dose-response analyses on β2AR agonist use stratified by duration of action (Liu et al., 2023; Tuominen et al., 2023). Both studies used DDDs as a cumulative measure of exposure. Regardless of exposure level, compared to nonuse, neither short- nor long-acting β2AR agonists were associated with PD incidence (Liu et al., 2023). Tuominen et al. (2023) reported an inverse association for different levels of β2AR agonist exposure in comparison to nonuse, and this association was strongest in the highest exposure group. An exception was the highest dose for ultra-long-acting β2AR agonists, which did not reach statistical significance.

Lag periods of different lengths between β2AR agonist exposure and PD diagnosis were applied in some studies, to control reverse causality. In Gronich et al. (2018), after applying a lag period of 2, 5, or 8 years and when users with <6 prescriptions or ≥6 prescriptions were compared to nonusers, formoterol was not associated with PD risk. By contrast, those with 6 or more salbutamol prescriptions had decreased PD risk with 2-, 5-, or 8-year lag periods. If salbutamol users had filled only <6 prescriptions, the reduced risk was significant only with a 2-year lag period. In Giorgianni

et al. (2020), compared to nonuse, the use of any β2AR agonist decreased PD risk with 0-, 1-, 2- and 3-year lag periods but no longer with a 5-year lag. In a Norwegian cohort study, when compared to nonuse, the use of any β2AR agonist significantly reduced PD risk for up to a 5-year lag period but no longer with a 7-year lag (Tuominen et al., 2023). When stratified by the duration of action, associations were nonsignificant with 2-, 5- or 7-year lags. In summary, drawing a straightforward conclusion is impossible due to different study designs but, with a longer lag period, the association seems to weaken.

In addition to using lag periods, Giorgianni et al. (2020) conducted stratified analyses by time since initiation of a β2AR agonist in relation to PD onset to determine whether it influences the results. PD risk decrease was strongest when a β2AR agonist was initiated 1-2 years before PD diagnosis (OR 0.75; 95% CI 0.64-0.88). Relative risk slightly weakened for β2AR agonists initiated 3-5 years before PD diagnosis (OR 0.81; 95% CI 0.69-0.94), and the association was no longer significant when drugs initiated 6-21 years before PD were considered. When analysis in a Danish case-control study was restricted to exposure occurring only within 5 years before PD diagnosis, compared to nonuse, use of any β2AR agonist during this period (ever use) was associated with reduced PD risk (Hopfner et al., 2019). However, when exposure from the last 5 years was ignored, ever use also resulted in decreased PD risk. These findings, along with application of a lag period in exposure assessment, suggest that obtaining decreased PD risk for β2AR agonist use is more likely when exposure occurs close to PD diagnosis.

Furthermore, long-term use of β2AR agonists for ≥3 years showed no association with a 5-year lag (Hopfner et al., 2019). However, without a lag, an inverse association similar to that with only <1 year of use emerged. Considering that lower PD risk was related to only short-term use of β2AR agonists (≤2 years) also in another case-control study (Giorgianni et al., 2020), the association may not be causal.

De Germay et al. (2020) evaluated whether the association between β2AR agonists and PD was modified by potential PD risk factors. They found an interaction between β2AR agonists and diabetes. In stratified

analyses, they observed increased PD risk among β2AR agonist users compared to nonusers in persons with diabetes but a decreased risk in β2AR agonist users compared to nonusers in those without diabetes. Salbutamol exhibited a similar trend except that associations were no longer statistically significant. A meaningful explanation for these findings is lacking. Possibly, those with diabetes have more regular contact with health care providers, and the result is due to detection bias.

Several studies have tried to capture the history of smoking. Smoking has been defined using smoking-related data from registers in numerous studies (de Germay et al., 2020; Giorgianni et al., 2020; Gronich et al., 2018; Searles Nielsen et al., 2018). Markers of smoking (inhaled corticosteroids, anticholinergics, and COPD) were used in (Hopfner et al., 2019), and education level was used as a proxy for smoking in (Mittal et al., 2017). These variables could have failed to fully capture the history of smoking. For example, according to Giorgianni et al. (2020), UK Clinical Practice Research Datalink contains information on smoking status; however, in a quarter of cases and controls, smoking status was unknown, which might have led to residual confounding. Searles Nielsen et al. (2018) had a comprehensive validated smoking variable with 100% positive predictive value but with poor sensitivity; that is, those classified as smokers are true smokers, but several true smokers are, however, missed (Desai et al., 2016; Searles Nielsen et al., 2018). Another solution to reduce the impact of smoking was to exclude persons with COPD in an attempt to have a similar proportion of smokers among users and nonusers of β2AR agonists (Tuominen et al., 2023).

β2AR agonists may be indirectly associated with decreased PD risk, and smoking has been proposed to mediate this association (Hopfner et al., 2020). Those who smoke have, in general, decreased PD risk, and smokers are prone to develop COPD, in which β2AR agonists are used to alleviate symptoms. Hopfner et al. (2020) also speculated that, since other drugs with no biologic plausibility of reducing PD risk were associated with decreased risk (Hopfner et al., 2019), indirect association is the most probable explanation.

In conclusion, despite the mechanistic evidence from Mittal et al.'s experimental study (2017), increasing numbers of epidemiological studies have yielded conflicting findings on PD risk from β2AR agonist use. The strength and direction of association in previous epidemiological studies may be driven by bias or result from indirect association through smoking. Heterogeneous study designs prevent direct comparison between studies. Studies often investigated the relationship between βAR antagonists and PD risk as well, so they were not solely designed for β2AR agonists. As for individual drugs, most studies focused on salbutamol, with mixed findings. The longer duration of action of β2AR agonists might play a role in PD risk reduction (Gronich et al., 2018; Tuominen et al., 2023), but the same was not evident in all studies (Giorgianni et al., 2020). Lag periods were applied in some settings, but findings are not uniform. Dose-response analyses do not seem to yield robust findings either.

Table 6. Summary of studies on the association between β2AR agonists and PD risk.

Reference, country, study type	**Population, data collection period**	**Exposure definition for β2AR agonist use, lag period, follow-up duration**	**N, mean age, sex**	**Relative risk (95% CIs) for ever use vs nonuse**
(Liu et al., 2023), Sweden, cohort	Residents of Sweden ≥40 years in 2013 without PD diagnosis before 30.06.2007	β2AR agonists during 01.07.2005-30.06.2007, stratified by duration of action Followed for PD onset 01.07.2007-31.12.2013; mean 6.1 years	Users of any β2AR agonist 430,885; 39% men Nonusers 4,752,999; 49% men At PD diagnosis 74.7 years	Any β2AR agonist: HR: 0.98 (0.87-1.09) Short-acting β2AR agonists: HR: 1.01 (0.91-1.12) Long-acting β2AR agonists: HR: 0.96 (0.84-1.09)
(Tuominen et al., 2023), Norway, cohort	Residents of Norway ≥25 years in 2005 without prescriptions for antiparkinsonian drugs in 2004	Minimum of two prescriptions for β2AR agonists during 2005-2019, stratified by duration of action Followed for PD onset 2005-2019	Users of short-acting 418,506; 42% men long-acting 360,467; 45% men ultra-long-acting* 68,953; 50% men Nonusers of β2AR, anticholinergics, or corticosteroids 2,600,086; 50% men. Age N/A	Short-acting β2AR agonists: HR: 0.84 (0.79-0.89) Long-acting β2AR agonists: HR: 0.85 (0.81-0.90) Ultra-long-acting* β2AR agonists: HR: 0.60 (0.49-0.73)

Table 6 (continued)

Reference, country, study type	**Population, data collection period**	**Exposure definition for β2AR agonist use, lag period, follow-up duration**	**N, mean age, sex**	**Relative risk (95% CIs) for ever use vs nonuse**
(Giorgianni et al., 2020), UK, nested case-control	Persons ≥50 years without previous PD and no prescriptions of β2AR agonist or β antagonist or antimuscarinic drug any time before cohort entry. Cases with PD onset ≥1 year after cohort entry and up to 10 matched controls 1995-2016	Any β2AR agonist and stratified by duration of action during 1995-2016 1-year lag Followed for PD onset until 2016; mean (SD) 7.6 (4.7) years	PD cases: 8,604 controls: 86,040 66.3, 64% men	Any β2AR agonist: OR: 0.83 (0.75-0.91) Short-acting β2AR agonists: OR: 0.83 (0.76-0.92) Long-acting β2AR agonists: OR: 0.89 (0.74-1.08)
(de Germay et al., 2020), France nested case-control	Cohort of persons ≥40 years. Cases with incident PD and 1:1 matched controls 2006-2017	Any β2AR agonist use during 1 year stratified by presence of diabetes 1-year lag Followed for PD onset 2008-2017	PD cases: 2,225 controls: 2,225 75.6, 51% men	With diabetes OR: 1.61 (1.02-2.55) Without diabetes OR: 0.75 (0.60-0.93)

Table 6 (continued)

Reference, country, study type	**Population, data collection period**	**Exposure definition for β2AR agonist use, lag period, follow-up duration**	**N, mean age, sex**	**Relative risk (95% CIs) for ever use vs nonuse**
(Hopfner et al., 2019), Denmark case-control	Cases with incident PD during 2000-2012 born before 1950 and 4 matched controls 1995-2012	Any β2AR agonist during 01.01.1995-1.7.2012	PD cases: 2,790 controls: 11,160 median age 73, 59% men	OR: 0.73 (0.63-0.85)
(Searles Nielsen et al., 2018), USA, case-control	Cases were US residents 66–90 years with PD diagnosis in 2009 without prior PD diagnosis since 2004. Controls without PD. 2004-2009	Salbutamol use during 2008-2009	PD cases: 48,295 controls: 52,324 cases 78.6; controls 76.4, N/A	OR: 0.97 (0.93-1.01)

Table 6 (continued)

Reference, country, study type	**Population, data collection period**	**Exposure definition for β2AR agonist use, lag period, follow-up duration**	**N, mean age, sex**	**Relative risk (95% CIs) for ever use vs nonuse**
(Gronich et al., 2018), Israel, nested case-control	Persons ≥20 years alive on 01.01.2004 without prior PD diagnosis and use of β2AR agonist or β antagonist. Cases with incident PD and 10 matched controls. 2004-2017	β2AR agonists by duration of action during 2004-2017 Followed for PD onset 01.01.2004-30.06.2017	PD cases: 11,314 controls: 113,140 74.7, 58% men	Short-acting β2AR agonists: OR: 0.89 (0.82-0.96) Long-acting β2AR agonists: OR: 0.84 (0.76-0.93) Ultra-long-acting* β2AR agonists: OR: 0.49 (0.25-0.92)
(Mittal et al., 2017), Norway, cohort	Entire population of Norway alive on 01.01.2004. Grouped to β2AR users and nonusers.	Salbutamol (inhaled and systemic) use in 2004-2007 Followed for PD onset 2005-2014	Users of β2AR agonists: 619,863 Nonusers: 4,066,119 N/A	RR: 0.66 (0.58-0.76)

*Vilanterol, olodaterol, indacaterol

Abbreviations: CI=confidence interval; HR=hazard ratio; N/A=not available; OR=odds ratio; PD=Parkinson's disease; RR=rate ratio; β2AR=β2-adrenoceptor

3 AIMS OF THE STUDY

The principal aim of this thesis was to study how DMARDs and β2AR agonists are associated with PD risk. Because the choice of appropriate exposure assessment period is important in risk factor studies, the incidence of muscle relaxant use in relation to PD diagnosis was investigated as an indicator of prodromal motor symptoms in PD.

The specific aims were to study:

1. the incidence of muscle relaxant use from four years before to four years after PD diagnosis in persons with PD and their comparison persons without PD (Study I)

2. the association between DMARDs and PD risk in persons with RA (Study II)

3. the association between inhaled β2AR agonists and PD risk in persons with asthma or COPD (Study III)

4 PARTICIPANTS AND METHODS

4.1 DERIVATION AND DATA SOURCES FOR FINPARK

This thesis used nationwide register-based data from the Finnish Parkinson's disease study (FINPARK). FINPARK includes all community-dwelling Finnish residents who received a special reimbursement for PD drugs (classification number 110) during 1996-2015 (N=29,942). For these individuals, seven comparison persons without PD were matched by age (+/- 1 year), sex, and hospital district, at the date of entitlement to reimbursement (N=209,594). Comparison persons were identified from the Social Insurance Institution (SII) database covering all residents of Finland. Comparison persons were not allowed to have the special reimbursement for PD drugs or purchases of dopaminergic PD drugs (ATC N04B) at any time before the referent person's date of entitlement to reimbursement or 12 months after or during the month of entitlement to reimbursement.

4.1.1 Eligibility for reimbursement for antiparkinsonian drugs

Persons who received a special reimbursement for PD drugs were identified from the Special Reimbursement Register. The SII reviews medical statements and, if predefined criteria are fulfilled, approves a special reimbursement. In terms of classification number 110 for PD drugs, diagnosis and evaluation of the need for pharmacotherapy must be conducted in a specialized neurology health care unit or by a neurologist in public or private health care. This medical statement for the SII must include anamnestic information and clinical assessment of symptoms such as the presence of rest tremor, bradykinesia, or rigidity. Persons with conditions other than PD may also be eligible for special reimbursement for PD drugs if treatment efficacy is proven for that condition. However, persons with intention or essential tremor as well as extrapyramidal symptoms due to antipsychotic drugs are ineligible.

4.1.2 Exclusion criteria for FINPARK

To further restrict FINPARK data to those who had clinically verified PD diagnosis, those individuals that had missing diagnosis codes or a code other than ICD-10 G20 recorded in the Special Reimbursement Register when reimbursement was granted were excluded (N=1,244) (Figure 3). Additionally, since sporadic PD among younger persons is rare, persons under age 35 at the time of entitlement to reimbursement were excluded (N=53) (Van Den Eeden et al., 2003).

Persons with diagnoses that have symptom types similar to PD ones within two years before or after the date they were eligible for reimbursement for PD drugs were excluded (N=6,962 Study I, N=6,456 Studies II and III). Exclusion diagnoses and their data sources are represented in Table 7. The proportion of persons excluded from the PD cohort was around 25%, which is in line with the literature on the proportion of falsely diagnosed PD cases (Harding et al., 2019; Wermuth et al., 2015). The total number of persons included with PD was 21,683 in Study I and 22,189 in Studies II and III. The date of first entitlement to reimbursement was considered as the date of PD diagnosis.

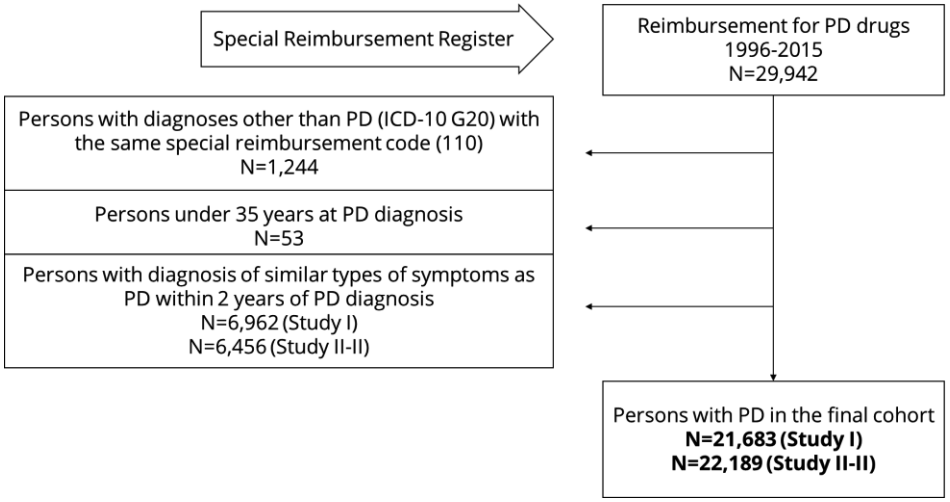


Figure 3. Identification of persons with Parkinson's disease (PD) in FINPARK.

The same exclusion criteria regarding diagnoses were employed consistently in both the PD and comparison cohort (Table 7). An exception was dementia in PD (ICD-10 F02.3), which was used as an additional exclusion criterion in Study I in both persons with and without PD. In Studies II and III, F02.3 was part of the exclusion criteria only in comparison persons. Dementia in PD was kept as an exclusion criterion in comparison persons to ascertain exclusion of PD from the comparison cohort, but it was removed from the PD cohort after reassessment of the exclusion criteria. The date of entitlement to reimbursement of the PD case was set as an index date for the referent set of matched comparison persons.

Table 7. Exclusion diagnoses for persons with PD. Exclusion diagnoses were the same for comparison persons except for F02.3 Dementia in PD, which was kept as an exclusion criterion throughout Studies I-III.

	Care Register for Health Care		**Special Reimbursement Register**
Exclusion diagnoses	**ICD-10**	**ICD-9**	**Classification number**
Alzheimer's disease	G30	3310A	307 along with ICD-10 G30
Dementia	F00-F03 (excluding F02.3 Dementia in PD in Studies II and III)	0461A, 2900A,2941A, 3310A, 3311A, 3334A, 4378A,	
Huntington disease	G10	3334A	
Secondary parkinsonism	G21	3321A	
Parkinsonism in diseases classified elsewhere	G22	0948X, 3321A	
Other degenerative diseases of the basal ganglia	G23	3330A	
Dystonia	G24	3339X	
Other extrapyramidal and movement disorders	G25	3331A, 3332A, 3333A, 3338X, 3339X	
Hereditary ataxia	G11	3340A, 3341A, 3342A	

Table 7 (continued)

	Care Register for Health Care		Special Reimbursement Register
Exclusion diagnoses	**ICD-10**	**ICD-9**	**Classification number**
Systemic atrophies primarily affecting the central nervous system in diseases classified elsewhere	G13	3318X, 3588X	
Other degenerative diseases of the nervous system, not elsewhere classified	G31	3311A, 3312X, 3318X	
Multiple sclerosis	G35	3400A	109, 157, 164, 303, 353
Multi-system degeneration	G90.3	3378X	

Abbreviations: ICD=international classification of diseases; PD=Parkinson's disease

4.1.3 Data sources

FINPARK contains data from several nationwide Finnish registers (Table 8). Data linkage across registers is possible due to personal identification numbers.

Data on entitlements to special reimbursement for drugs due to diseases considered serious and chronic such as RA or asthma is derived from the Special Reimbursement Register (Table 8). Reimbursement at the higher or lower special rate or limited basic rate can be granted only on medical grounds, and predefined criteria must be fulfilled. A written medical statement must be sent to the SII by a physician. Reimbursement entitlement can be for a specified period or without restrictions, and all entitlements are recorded in the register regardless of drug purchases. Since 2000, in this register, the diagnosis code for which the

reimbursement was granted has been increasingly recorded in connection with the classification code.

The Hospital Discharge Register, which was replaced by the Care Register for Health Care in 1994, includes data on reasons for inpatient hospital admission, admission dates, and discharge diagnoses (Table 8) (Sund, 2012). This thesis used information therein since 1972. Diagnoses are recorded as International Classification of Diseases (ICD) diagnosis codes, using ICD-8, ICD-9, and ICD-10 versions. Data on specialized outpatient care in public hospitals has been available since 1998. According to a validation study (Sund, 2012), the positive predictive value for common diagnoses varied between 75-99%.

Since 1995, all drugs, emollient creams, or clinical nutrients reimbursed by the National Health Insurance Scheme and dispensed in community pharmacies have been recorded in the Prescription Register (Table 8) (Furu et al., 2010). Drugs are categorized according to the World Health Organization (WHO) anatomical therapeutic chemical (ATC) classification system. In addition to dispensing date, information on amount of drug purchases as DDDs is available. DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults (WHOCC - Definition and general considerations, 2022). Non-reimbursed or over-the-counter drugs and drug use in hospitals or in public nursing homes are unrecorded. The Prescription Register lacks information on the indication for drug use.

In this thesis, information on death and occupational socioeconomic class is from Statistics Finland, and information on all primary cancers in Finland is from the Finnish Cancer Registry (Table 8).

Table 8. Description of FINPARK data sources used in this thesis.

Data sources and time period	**Register maintainer**	**Data utilized in this thesis**
Care Register for Health Care 1972-2016	Finnish Institute of Health and Welfare	Hospital admission/visit dates, reason for hospital stays (ICD-codes) in inpatient hospital care in both public and private hospitals, specialized health care outpatient visits, reason for admission
Special Reimbursement Register 1972-2016	Social Insurance Institution of Finland	Special reimbursement code for drugs for chronic diseases, information on diagnosis (ICD-8/9/10 code, missingness before 2000), date of entitlement
Prescription Register 1995-2016	Social Insurance Institution of Finland	All reimbursed prescription drugs, dispensing date, ATC code, amount of drug purchase as DDDs
Statistics Finland 1972-2016	Statistics Finland	Information on death, occupational socioeconomic position
Finnish Cancer registry 1972-2016	Cancer Society of Finland	All diagnosed cancer cases, diagnosis date

Abbreviations: ATC=anatomical therapeutic chemical; DDD=defined daily dose; ICD=international classification of diseases

4.2 DRUG EXPOSURE

4.2.1 Study I

Data on muscle relaxant use was extracted from the Prescription Register during 1995-2016. Muscle relaxants were categorized according to the two ATC groups: M03A, peripherally acting agents; and M03B, centrally acting agents (Table 9).

Table 9. Muscle relaxants identified from the Prescription Register during 1995-2016.

	Drug: ATC code
Peripherally acting agents: M03A	Botulinum toxin: M03AX01
Centrally acting agents: M03B	Methocarbamol: M03BA03 Carisoprodol, combinations excluding psycholeptics: M03BA52 Methocarbamol, combinations excluding psycholeptics: M03BA53 Chlorzoxazone, combinations excluding psycholeptics: M03BB53 Orphenadrine (citrate): M03BC01 Orphenadrine, combinations: M03BC51 Baclofen: M03BX01 Tizanidine: M03BX02

Abbreviations: ATC=anatomical therapeutic chemical

4.2.2 Study II

Data on DMARD use was extracted from the Prescription Register since 1995 until the index date, i.e., PD diagnosis date. DMARDs were selected according to ATC codes and were categorised into five classes: sulfasalazine, methotrexate, chloroquine or hydroxychloroquine, gold preparations, and immunosuppressants including biologic DMARDs (Table 10). In sensitivity analysis, biologic DMARDs were handled as a separate category. Information on corticosteroid use (methylprednisolone ATC: H02AB04, prednisolone ATC: H02AB06 and prednisone ATC: H02AB07) was also retrieved.

Table 10. Definition of DMARDs.

	Drug: ATC code
Sulfasalazine	Sulfasalazine: A07EC01
Methotrexate	Methotrexate: L04AX03
Chloroquine or hydroxychloroquine	Chloroquine: P01BA01 Hydroxychloroquine: P01BA02
Gold preparations	Sodium aurothiomalate: M01CB01 Auranofin: M01CB03
Immunosuppressants	Mycophenolic acid: L04AA06 Leflunomide: L04AA13 Ciclosporin: L04AD01 Azathioprine: L04AX01 Biologic DMARDs: • Abatacept: L04AA24 • Etanercept: L04AB01 • Adalimumab: L04AB04 • Certolizumab pegol: L04AB05 • Golimumab: L04AB06 • Anakinra: L04AC03

Abbreviations: ATC=anatomical therapeutic chemical; DMARD=disease-modifying antirheumatic drug

4.2.3 Study III

Data on β2AR agonist exposure was extracted from the Prescription Register since 1995 until three years before the index date, i.e., PD diagnosis date. β2AR agonists were categorized according to their therapeutic duration of action into short-acting and long-acting, and use was defined with ATC codes (Table 11). Combination products with corticosteroids and anticholinergics were included. Furthermore, data on exposure to inhaled corticosteroids and anticholinergics was separately extracted to observe general exposure to other drugs typically used in asthma or COPD.

Table 11. Definition of inhaled β2AR agonists, corticosteroids, and anticholinergics.

	Drug: ATC code
Inhaled β2AR agonists	
Short-acting	Salbutamol: R03AC02, R03AL02 Terbutaline: R03AC03 Fenoterol: R03AC04, R03AL01
Long-acting	Salmeterol: R03AC12, R03AK06 Formoterol: R03AC13, R03AK07, R03AK08, R03AK11, R03AL05 Indacaterol: R03AC18, R03AL04 Olodaterol: R03AC19 Vilanterol (only in combinations): R03AK10, R03AL03
Inhaled corticosteroids	Beclometasone: R03BA01, R03AK08 Budesonide: R03BA02, R03AK07 Fluticasone propionate: R03BA05, R03AK06, R03AK11 Mometasone: R03BA07 Ciclesonide: R03BA08 Fluticasone furoate: R03AK10

Table 11 (continued)

	Drug: ATC code
Inhaled anticholinergics	
Short-acting muscarinic antagonist	Ipratropium bromide: R03BB01, R03AL01, R03AL02 Oxitropium bromide: R03BB02
Long-acting muscarinic antagonist	Tiotropium bromide: R03BB04 Aclinidium bromide: R03BB05, R03AL05 Glycopyrronium bromide: R03BB06, R03AL04 Umeclidinium bromide: R03BB07, R03AL03

Abbreviations: ATC=anatomical therapeutic chemical; β2AR=β2-adrenoceptor

4.3 STUDY DESIGNS

4.3.1 Study I

Study I was a cohort study in which the incidence of muscle relaxant use was evaluated in persons with and without PD from four years before until four years after PD diagnosis. The time of PD diagnosis of PD cases was set as an index date for referent comparison persons. The FINPARK cohort was restricted to persons with PD diagnosed during 2000-2015 (N=18,233) and to their comparison persons (N=127,505) (Table 12). Persons diagnosed with PD before 2000 were excluded to ensure that all participants had adequate follow-up time after a one-year washout period.

Table 12. Formation of study cohort in Study I.

	Persons with PD	**Comparison persons without PD**
Initial number of persons	21,683	151,639
PD diagnosis during 2000-2015	18,233	127,505
Exclusions		
Muscle relaxant use during 1-year washout period	767	4,698
Long-term hospitalization/ institutionalization during 1-year washout period	16	113
Final sample size	17,450	122,694

Abbreviations: PD=Parkinson's disease

A one-year washout period starting five years before index date was used to exclude prevalent users (Figure 4). Additionally, persons who had been hospitalized or institutionalized more than six months during the

washout period or over 90 days on the last day of washout were excluded. The final study population included 17,450 persons with PD and 122,694 comparison persons (Table 12). Incident users were persons who had no purchases during the washout but initiated using any of the muscle relaxants during the eight-year follow-up period. Only the first initiation after washout was included in the analysis. The follow-up was censored for any of the following reasons: initiation of muscle relaxant use, hospitalization of ≥90 days, death, or end of study on December 31, 2016 (Figure 4). Comorbidities were measured at the time of index date.

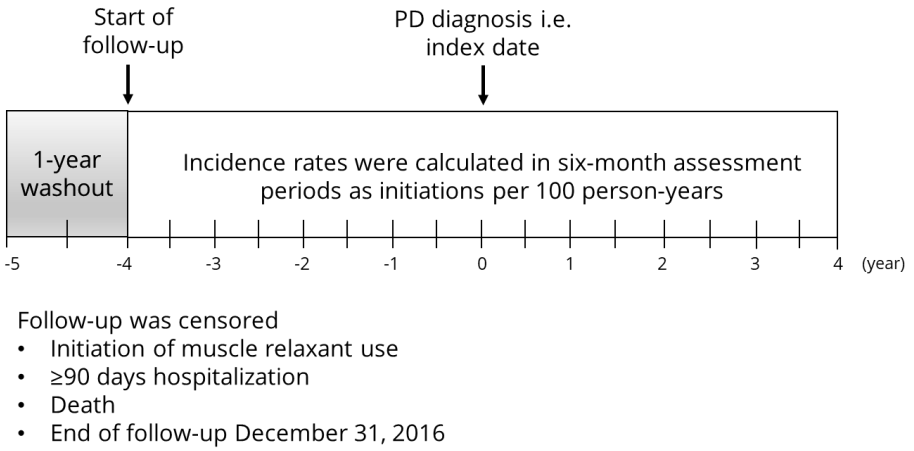


Figure 4. Design of Study I. PD=Parkinson's disease

4.3.2 Studies II and III

Studies II and III were both nested case-control studies conducted within FINPARK. PD cases diagnosed during 1996-1998 were excluded since drug exposure data was extracted from the beginning of the Prescription Register in 1995 and a 3-year lag was applied. A lag of three years was supported by Study I results. A lag period means that drug use during the lag was excluded in the main analyses (Figure 5).

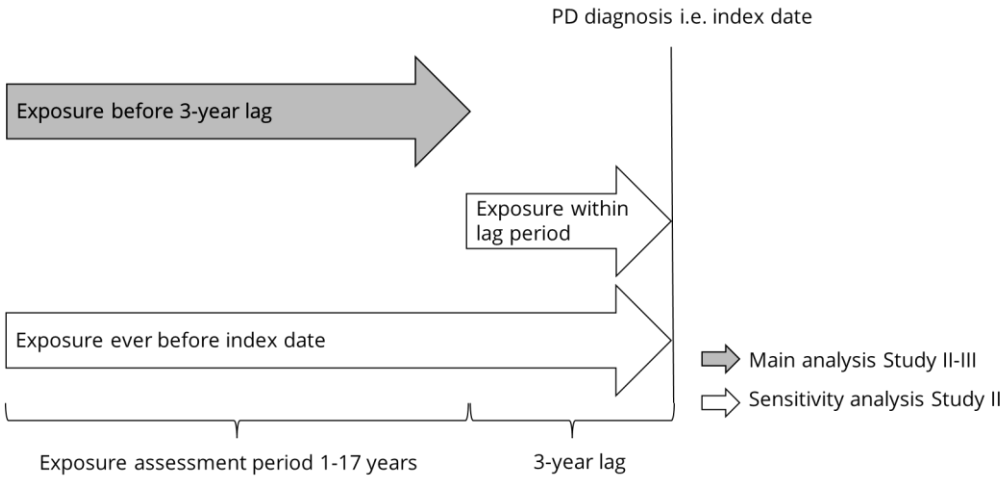


Figure 5. Different exposure time windows in Study II and use of lag period in Study III. PD=Parkinson's disease

In Study II, PD cases were further restricted to persons diagnosed with RA at least three years before PD diagnosis and in Study III to persons with either asthma or COPD (Table 13). RA, asthma, and COPD were identified from the Finnish Care Register for Health Care and Special Reimbursement Register, as described in Table 14. Diagnosis date for RA or asthma and/or COPD was the earliest event either for hospitalization or specialized health care outpatient visit or for entitlement to receive reimbursement for drugs used in these conditions.

For PD cases, up to seven controls were rematched from the 209,594 comparison persons from the original FINPARK study population, prior to application of any exclusion criteria. At first, comparison persons were restricted to those with RA (N=5,864) for Study II and those with asthma/COPD (N=30,135) for Study III. In Study II, controls were matched by age (±2 years), sex, university hospital district, and RA duration (±2 years). In Study III, matching was by age (±2 years), sex, pulmonary diagnosis type (asthma, COPD, both asthma and COPD), duration of asthma/COPD diagnosis (± 3 years), and university hospital district. Exclusion criteria as described in chapter 4.1.2 were applied for controls, during the matching procedure. In both studies, the index date was defined as PD diagnosis date or the corresponding date for controls

without PD. In total, 315 cases and 1,571 controls with RA were included in the final population in Study II and 1,406 cases and 8,630 controls with asthma/COPD in Study III (Table 13).

Table 13. Formation of the final study population in Studies II and III.

	Study II	**Study III**
Initial number of PD cases	22,189	22,189
Exclusions		
PD diagnosis before 1999	2,621	2,621
No RA	19,101	-
No asthma/COPD	-	17,197
RA ≤3 years before PD diagnosis	149	-
Asthma/COPD ≤3 years before PD diagnosis	-	949
Unmatched PD cases	3	16
Final number of PD cases	**315**	**1,406**
Number of matched controls	**1,571**	**8,630**

Abbreviations: COPD=chronic obstructive pulmonary disease; PD=Parkinson's disease; RA=rheumatoid arthritis

Table 14. Definition of RA (Study II), asthma and COPD (Study III).

ICD code or classification number	Data source and time period
Rheumatoid arthritis	
ICD-10: M05-M059, M06, M061	Finnish Care Register for Health Care 1996-2012
ICD-9: 714, 7140A, 7141A, 7143A, 7143B, 7143X	Finnish Care Register for Health Care 1987-1995
Special reimbursement for medication: classification number 202 along with one of the abovementioned ICD-9 or ICD-10 codes	Special Reimbursement Register 1972-2012
ICD-8: 71200, 71210, 71238, 71239 were used to acquire the possible earlier date of RA diagnosis in case a person also had a record of either an ICD-10 or ICD-9 code.	Finnish Care Register for Health Care 1972-1986
Asthma	
ICD-10: J45*, J46*	Finnish Care Register for Health Care 1996-2012
ICD-9: 493*	Finnish Care Register for Health Care 1987-1995
ICD-8: 49300, 49302, 49308, 49309	Finnish Care Register for Health Care 1972-1986
Special reimbursement for medication: classification number 203 or 210 along with one of the abovementioned ICD-9 or ICD-10 codes	Special Reimbursement Register 1972-2012

Table 14 (continued)

ICD code or classification number	Data source and time period
COPD	
ICD-10: J43*, J44*	Finnish Care Register for Health Care 1996-2012
ICD-9: 4912A, 4912B, 492, 4920A, 4928A, 4928X	Finnish Care Register for Health Care 1987-1995
ICD-8: 49104, 49201, 49202, 49209	Finnish Care Register for Health Care 1972-1986
Special reimbursement for medication: classification number 203 or 210 along with one of the abovementioned ICD-9 or ICD-10 codes	Special Reimbursement Register 1972-2012
Asthma and COPD	
Abovementioned definitions for both asthma and COPD were met.	

Abbreviations: COPD=chronic obstructive pulmonary disease; ICD=international classification of diseases; RA=rheumatoid arthritis
*Indicates that all diagnosis codes that begin with these characters are included.

In Study II, data on DMARD exposure before the 3-year lag was extracted for the main analysis. In sensitivity analyses, DMARD use within the 3-year lag and use at any time before index date without the lag was obtained (Figure 5). A user was defined as someone having at least one purchase during each observation period. Additionally, exposure histories for different DMARD classes before the 3-year lag were obtained.

In Study III, dose-response analyses examined PD risk and β2AR agonist exposure until the beginning of a 3-year lag period. The study population was restricted to three subsets: users of short-acting, long-acting, and any β2AR agonist, i.e., users of short- and/or long-acting β2AR agonists (Table 15). Due to the matched design, after nonusers among the study population were excluded, unmatched PD cases and controls were excluded. The cumulative dose was calculated using DDDs. Furthermore, the number of purchase years was calculated. First, purchases were

divided according to dispensing date into windows of one year (365 days) in relation to index date, after which purchase years were summed to get an estimate of years with β2AR agonist exposure. Purchase years were not required to be consecutive, and one year of use included at least one purchase. Cumulative DDDs were divided with the sum of purchase years to get an average exposure per purchase year, i.e., annual exposure (DDD/year).

Table 15. Final study population for dose-response analyses in Study III.

	Short-acting β2AR agonist	**Long-acting β2AR agonist**	**Any β2AR agonist**
Initial number of users before 3-year lag	8,359	4,862	8,669
Excluded due to unmatched cases and controls	983	1,973	818
Final number of users	**7,376**	**2,889**	**7,851**

Abbreviations: β2AR=β2-adrenoceptor

4.4 COVARIATES

For each covariate, definitions and measurement time points are described in Table 16. Covariates were retrieved until the index date (Studies I and II) or until the beginning of the 3-year lag (Studies II and III), unless otherwise specified. Definitions can vary between studies. Covariates were chosen based on their possible PD association and as markers of general health status that could impact drug exposure.

Table 16. Definition of covariates in Studies I-III.

Covariate	Data source	Definition	Measurement time point	Study
Asthma or COPD	Special Reimbursement Register	Special reimbursement: classification number 203	Since 1972	I
	Care Register for Health Care	Hospital diagnosis ICD-8: 493 ICD-9: 493, 4912A, 4960A ICD-10: J44–J46	ICD-8: 1972-1986 ICD-9: 1987-1995 ICD-10: hospitalizations since 1996, specialized health care outpatient visits since 1998	II
	Special Reimbursement Register	Special reimbursement: classification number 203	Since 1972	
Cancer history	IARC CRG Tools, Cancer Register	Hospital diagnosis ICD-10: C00-C97	Since 1972	II & III
Cardiovascular diseases	Special Reimbursement Register	Special reimbursement: classification number 201, 205, 206, 207	Since 1972	I
	Special Reimbursement Register	Special reimbursement: classification number 201, 205, 206, 207, 213, 280	Since 1972	II & III

Table 16 (continued)

Covariate	Data source	Definition	Measurement time point	Study
Diabetes	Special Reimbursement Register	Special reimbursement: classification number 103	Since 1972	I-III
	Care Register for Health Care	Hospital diagnosis ICD-8: 250, 25101 ICD-9: 250 (Studies II & III), 2510 and 2518 (Study II) ICD-10: E10–E14	 ICD-8: 1972-1986 ICD-9: 1987-1995 ICD-10: hospitalizations since 1996, specialized health care outpatient visits since 1998	 II II & III
Head injury	Care Register for Health Care	Hospital diagnosis ICD-8: 800–804, 830, 850–854, 870–873, 904, 906, 910, 920, 921, 950, 951 ICD-9: 800–803,830, 8480, 850–854, 870–873, 918, 920, 921, 9250, 9251, 950, 951, 9590 ICD-10: S00–S09	 ICD-8: 1972-1986 ICD-9: 1987-1995 ICD-10: hospitalizations since 1996, specialized health care outpatient visits since 1998	 II

Table 16 (continued)

Covariate	Data source	Definition	Measurement time point	Study
Traumatic brain injury	Care Register for Health Care	Hospital diagnosis ICD-9: 850-854 ICD-10: S06	ICD-9: 1987-1995 ICD-10: hospitalizations since 1996, specialized health care outpatient visits since 1998	III
Rheumatoid arthritis and connective tissue diseases	Special Reimbursement Register	Special reimbursement: classification number 202	Since 1972	I
Stroke	Care Register for Health Care	Hospital diagnosis ICD-8: 430-434 ICD-9: 430–432 ICD-10: I60-I64	ICD-8: 1972-1986 ICD-9: 1987-1995 ICD-10: hospitalizations since 1996, specialized health care outpatient visits since 1998	II II & III

Table 16 (continued)

Covariate	Data source	Definition	Measurement time point	Study
Substance abuse	Care Register for Health Care	Hospital diagnosis ICD-8: 291, 3031, 3032, 3039, 980 ICD-9: 291, 292, 303-305, 980, 3575, 3594, 4255, 5353, 7903, 5710A, 5711A, 5712A, 5713A, 5713X, 5771C, 5771D and reason for admission: substance abuse 33, 71–75 ICD-10: F10-F19, G31.2, G62.1, G72.1, I42.6, K29.2, K70, K86.0, R78.0, T51.0, T51.1, T51.9, X45 and reason for admission: substance abuse 33, 71–75	ICD-8: 1972-1986 ICD-9: 1987-1995 ICD-10: hospitalizations since 1996, specialized health care outpatient visits since 1998	II II & III
	Prescription Register	Drugs for alcohol or opioid dependence (ATC: N07BB, N07BC)	Since 1995	II & III

Table 16 (continued)

Covariate	Data source	Definition	Measurement time point	Study
Socioeconomic position	Statistics Finland	Self-employed persons, Upper-level employees with administrative, managerial, professional, and related occupations, Lower-level employees with administrative, managerial, professional, and related occupations, Manual workers, Pensioners, Others (students, long-term unemployed, others not classified elsewhere, socioeconomic status unknown or missing)	1972-1994	III

Abbreviations: ATC=anatomical therapeutic chemical; ICD=international classification of diseases

4.5 STATISTICAL ANALYSES

In Studies I-III, descriptive analyses for between-group comparisons were performed by a t-test for normally distributed continuous variables and a Mann-Whitney U test for non-normally distributed ones. A Chi-squared test was performed on categorical variables. Statistical analyses were performed using SAS 9.4 software as well as SPSS statistic 25 (Study I) and Stata MP14.0 (Studies II and III).

In Study I, IRs per 100 person-years were calculated for both persons with and without PD in six-month assessment periods (Figure 4). Incidence rate ratios (IRRs) with 95% CIs were calculated with Poisson regression by comparing IR differences between persons with PD and comparison persons without PD. Analyses were conducted for muscle relaxant use in general and, in particular, for the two most frequently used muscle relaxants, tizanidine and orphenadrine, separately. Orphenadrine here also refers to its combination preparation with paracetamol.

In Study II, associations between DMARD use and PD risk were studied with conditional logistic regression, and results were reported as ORs with 95% CIs. Exposure to individual DMARD categories before the 3-year lag, use within the lag period, or any use before index date was compared to nonuse during that specific exposure period. Associations between different exposure histories for DMARDs before the 3-year lag and PD risk were compared to sulfasalazine since it was the most frequent exposure category. Factors included in the adjusted model were asthma/COPD, cancer history, cardiovascular diseases, diabetes, head injury, stroke, and substance abuse. A detailed description of these covariates is provided in Table 16.

In Study III, associations between the use of short- or long-acting β2AR agonists and PD risk were studied with conditional logistic regression, to obtain ORs with 95% CIs, and use was compared to nonuse before the 3-year lag. For dose-response analyses, continuous variables, cumulative DDDs, as well as annual exposure to short-, long-acting and any β2AR agonists were categorized into quartiles in primary analyses and into tertiles in sensitivity analyses. In conditional logistic regression analyses,

the lowest quantile was used as a reference. The adjusted model accounted for cancer history, cardiovascular diseases, diabetes, socioeconomic position, stroke, substance abuse, and traumatic brain injury. For a detailed description of these covariates, see Table 16. In the sensitivity analysis, this model was further adjusted for inhaled corticosteroids and anticholinergics (Table 11). For statistically significant associations, modification by pulmonary diagnosis type was evaluated by adding an interaction term, exposure*pulmonary diagnosis type, in the adjusted model. Stratified analysis according to pulmonary diagnosis type was conducted for long-acting β2AR agonists since the significance level for interaction $P<0.1$ was met. An additional analysis was performed using a Kruskal-Wallis test to determine whether differences exist in cumulative DDDs and annual exposure to short-, long-acting, or any β2AR agonists between individuals with different pulmonary diagnosis types (asthma, COPD, asthma and COPD).

4.6 ETHICAL CONSIDERATIONS

Data was pseudonymized before submission to the research team, and study participants were not contacted. Therefore, according to Finnish legislation (including Personal Data Act 23/1999, Act on the Openness of Government Activities 621/1999 and Act on the Secondary Use of Health and Social Data 552/2019 (and a previous Act in the National Health care registers, 556/1989, for which no official English translation is available) the study was granted exemption from requiring ethics approval or informed consent. Only persons with permission from register maintainers have access to this data.

5 RESULTS

5.1 STUDY I

At the time of index date, the mean age of muscle relaxant users was 67.4 (SD 10.2) and of nonusers 71.6 (SD 9.5); at the time of initiation, the mean age of users was 66.8 (SD 10.4). In the entire study population, over half (55.9%) were men. The use of muscle relaxants was more common among women (Table 17). Cardiovascular diseases were the most common comorbidities, followed by diabetes, asthma/COPD, as well as RA and connective tissue diseases (Figure 6). Both cardiovascular diseases and diabetes were more common among nonusers with and without PD than among users. Compared to nonusers, users with and without PD were more likely to have a history of asthma/COPD.

Table 17. General characteristics of the population in Study I measured at the time of Parkinson's disease (PD) diagnosis, i.e., index date. Given as mean (standard deviation) for age and n (%) for others.

	PD N=17,450			**Non-PD N=122,694**		
	Users N=3,424	**Nonusers N=14,026**	**P**	**Users N=18,639**	**Nonusers N=104,055**	**P**
Age	67.3 (9.9)	71.8 (9.4)	<0.0001	67.5 (10.2)	71.5 (9.5)	<0.0001
Sex			<0.0001			<0.0001
Men	1,700 (49.7)	8,068 (57.5)		9,533 (51.2)	59,058 (56.8)	
Women	1,724 (50.4)	5,958 (42.5)		9,106 (48.9)	44,997 (43.2)	

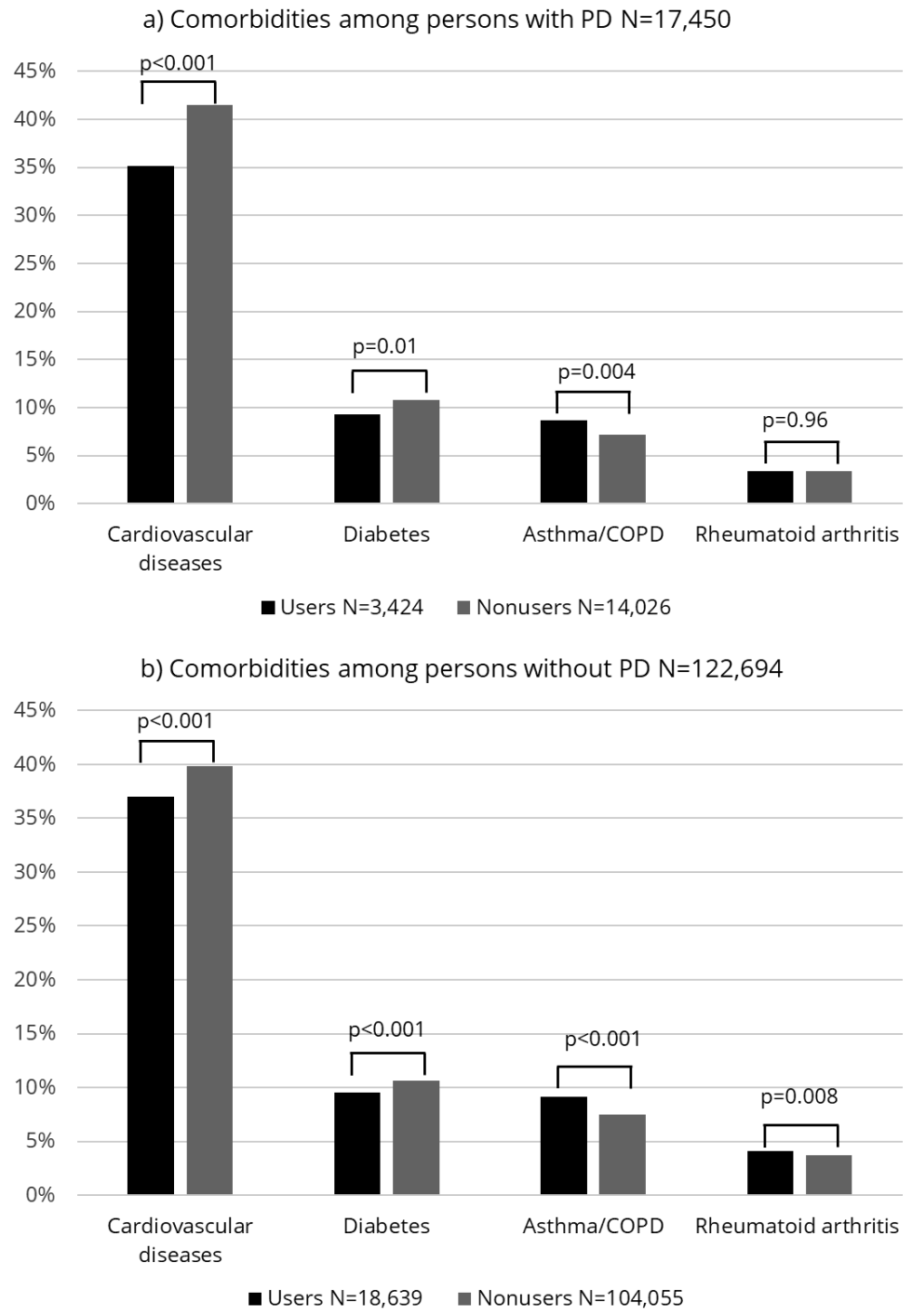


Figure 6. Comorbidities measured at the time of index date between users and nonusers of muscle relaxants a) among persons with Parkinson's disease (PD) and b) among persons without PD.

During the 8-year follow-up, 19.6% of persons with PD (3,424/17,450) and 15.2% of the comparison persons without PD (18,639/122,694) initiated the use of a muscle relaxant (Table 18). The three most initiated muscle relaxants in both persons with and without PD were tizanidine, covering 64% of all initiations in the entire study population, followed by an orphenadrine combination with paracetamol and orphenadrine.

Table 18. Initiated muscle relaxants among users with and without Parkinson's disease (PD).

	Users with PD N=3,424; (n %)	**Users without PD N=18,639; (n %)**
Tizanidine	2,136 (62.4)	11,977 (64.3)
Orphenadrine, combinations with paracetamol	749 (21.9)	4,160 (22.3)
Orphenadrine (citrate)	429 (12.5)	2,148 (11.5)
Carisoprodol, combinations excluding psycholeptics	57 (1.66)	232 (1.24)
Baclofen	35 (1.02)	65 (0.35)
Botulinum toxin	11 (0.32)	14 (0.08)
Chlorzoxazone, combinations excluding psycholeptics	6 (0.18)	42 (0.23)
Methocarbamol	1 (0.03)	1 (0.005)

Muscle relaxant initiations were more common among persons with PD. For the entire 8-year follow-up period, the incidence of muscle relaxant use was higher in persons with PD than in persons without PD (IRR 1.29; 95% CI 1.25-1.34): 3.03 initiations per 100 person-years among persons with PD and 1.29 initiations per 100 person-years among persons without PD.

Compared to persons without PD, among persons with PD, the IR per 100 person-years of any muscle relaxant use was significantly higher three years before PD diagnosis until six months after (Figure 7). Incidence difference was largest at the time of PD diagnosis (IRR 2.04; 95% CI 1.81-2.30), with 4.5 initiations per 100 person-years among persons with PD compared to 2.19 among those without PD. The IR for tizanidine was higher in persons with PD from two years before PD diagnosis until six

months after. For orphenadrine (including a combination product with paracetamol), it was similar from two years before but until the time of PD diagnosis. Incidence difference was the highest at the time of PD diagnosis for both tizanidine (IRR 2.07; 95% CI 1.79-2.39) and orphenadrine (IRR 1.96; 95% CI 1.62-2.36).

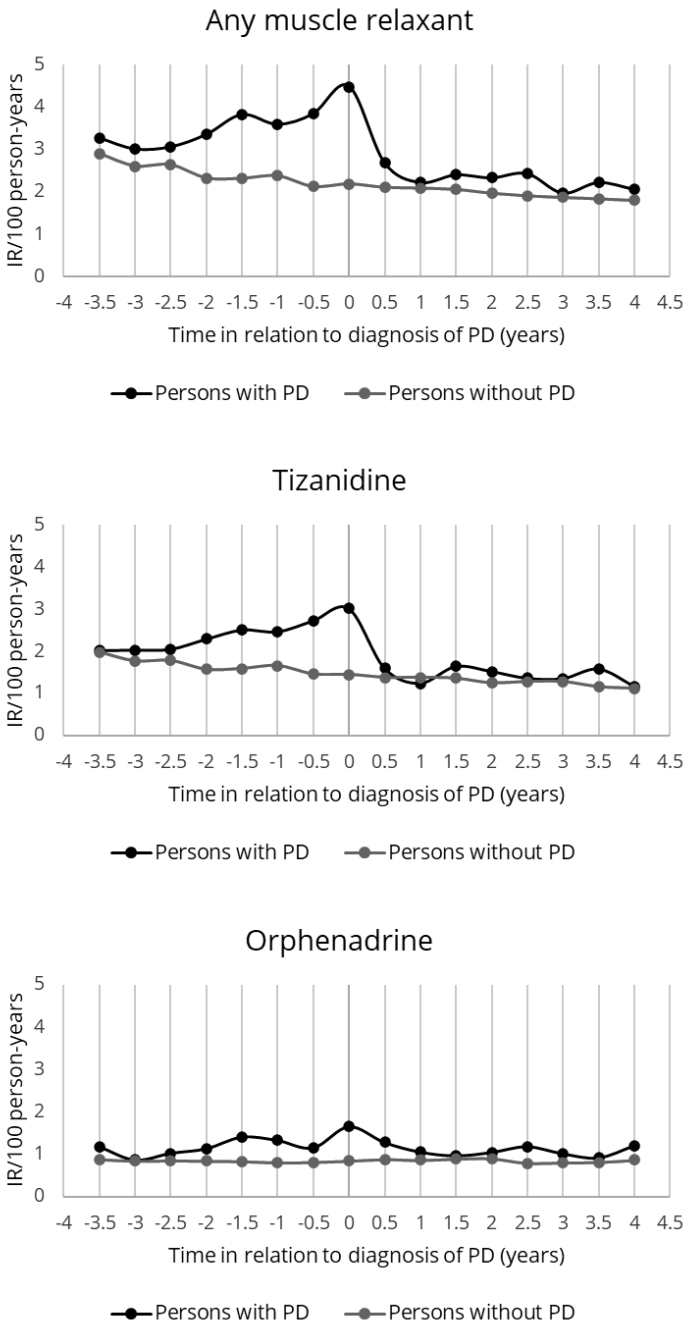


Figure 7. Incidence rates (IRs) for use of any muscle relaxant, tizanidine, and orphenadrine in persons with and without Parkinson's disease (PD) from four years before to four years after PD diagnosis. Zero refers to the time of PD diagnosis, i.e., index date.

5.2 STUDY II

PD cases and their matched controls with RA were on average 73 years old on index date, and the majority (>60%) of them were women (Table 19). Cardiovascular diseases were the most common comorbidities among PD cases (43.2%) and controls (40.7%) and, between these two groups, the prevalence of different comorbidities was similar (Figure 8).

Table 19. General characteristics of population in Study II.

	PD cases N=315	**Matched controls N=1,571**
Age; mean (SD)	73.1 (8.2)	73.1 (7.7)
Sex; n (%)		
Men	116 (36.8)	539 (34.3)
Women	199 (63.2)	1,032 (65.7)
Duration of rheumatoid arthritis on index date; median (IQR)	12.6 (8.4-20.5)	11.6 (7.5-19.2)

Abbreviations: IQR=interquartile range; PD=Parkinson's disease; SD=standard deviation

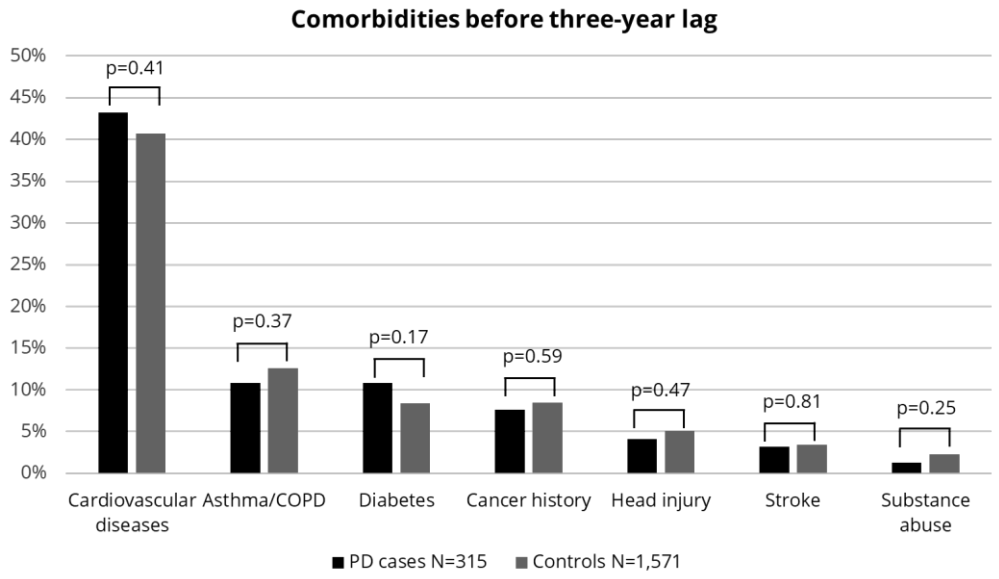


Figure 8. Different covariates between Parkinson's disease (PD) cases and matched controls with rheumatoid arthritis.

In the main analysis, the three most used DMARDs were sulfasalazine, methotrexate, and chloroquine/hydroxychloroquine (Figure 9). The least used DMARD class comprised immunosuppressants including biologic DMARDs. Chloroquine/hydroxychloroquine exposure was more common among controls (44.8%) than among PD cases (37.5%); otherwise, DMARD purchase distribution was similar.

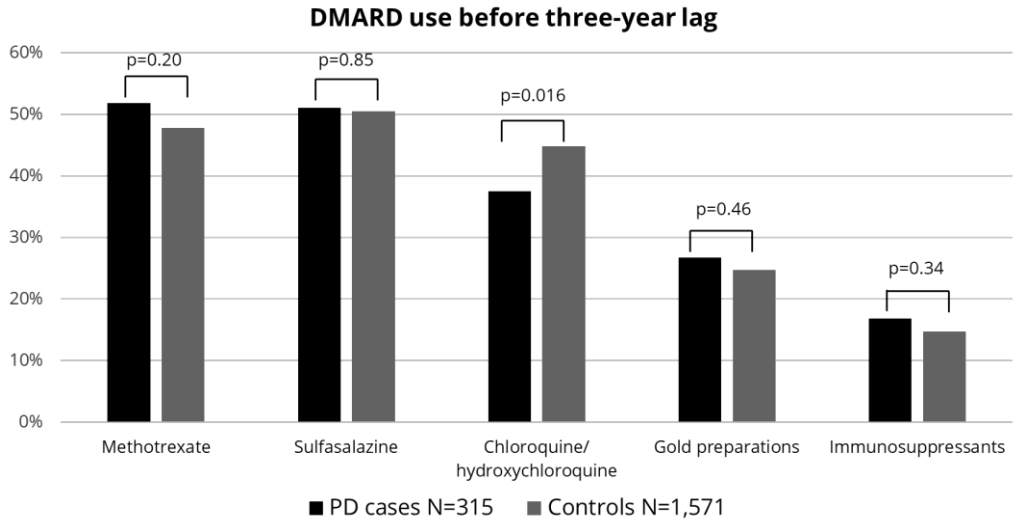


Figure 9. Exposure to disease-modifying antirheumatic drugs (DMARDs) before the 3-year lag among Parkinson's disease (PD) cases and matched controls with rheumatoid arthritis.

The use of different DMARD classes was not associated with PD risk in the main analysis except for the use of chloroquine/hydroxychloroquine, which was associated with reduced PD risk (adjusted odds ratio (aOR) 0.74; 95% CI 0.56-0.97) (Figure 10). In a sensitivity analysis, the use of chloroquine/hydroxychloroquine at any time before index date was also associated with decreased PD risk (aOR 0.69; 95% CI 0.53-0.89). No associations were evident for DMARDs when use only during lag period was considered.

Corticosteroid use before the 3-year lag was common in PD cases (66.7%) and controls (67.6%), and their use was not associated with PD risk in any exposure time window. Different exposure histories for DMARDs

before the 3-year lag when compared to sulfasalazine were not associated with PD risk.

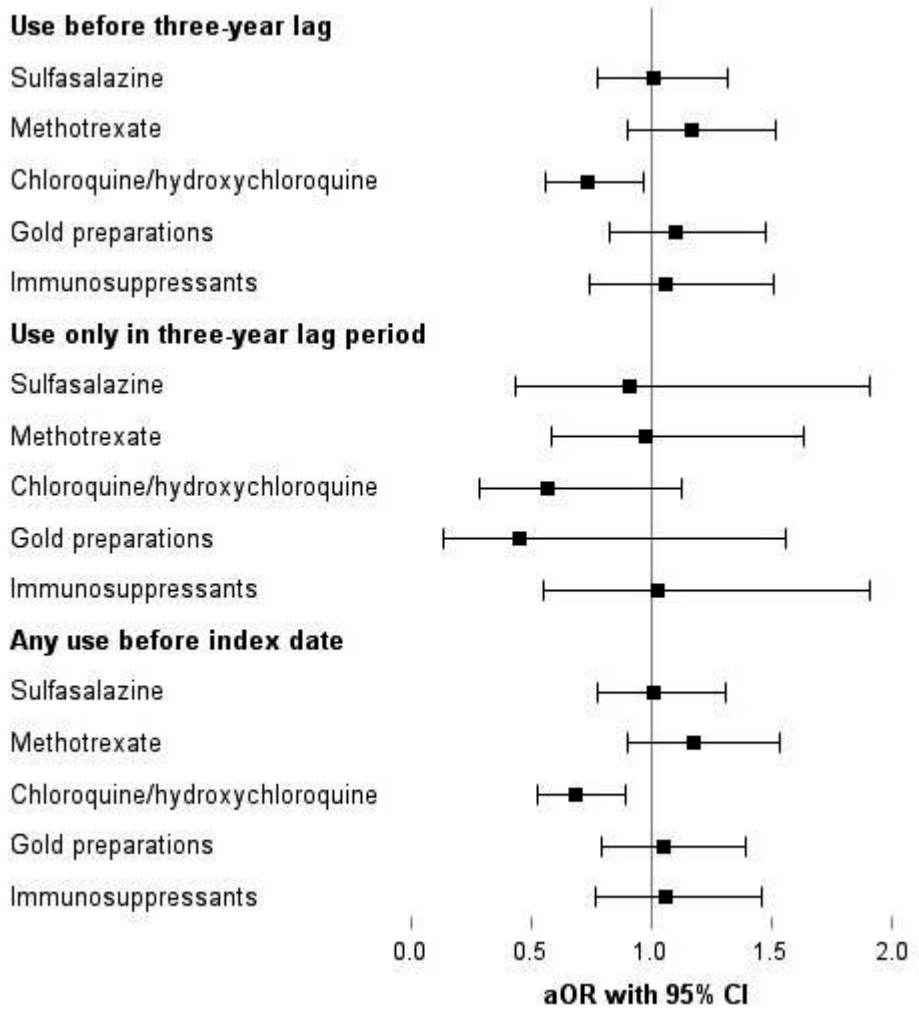


Figure 10. Adjusted odds ratios (aORs) with 95% confidence intervals (CIs) for the model evaluating associations between disease-modifying antirheumatic drugs and Parkinson's disease risk in different exposure time windows.

5.3 STUDY III

PD cases and their matched controls with asthma/COPD were, on average, aged 73 on index date, and over 74% had only an asthma diagnosis (Table 20). Having both asthma and COPD diagnoses was more common than having only COPD. Cardiovascular diseases were the most common comorbidities among PD cases (47.9%) and controls (47.4%). The prevalence of different comorbidities was similar except for cancer history, which was more frequent among controls (9.4%) than in PD cases (7.6%) (Figure 11).

Table 20. General characteristics of population in Study III.

	PD cases N=1,406	**Matched controls N=8,630**
Age; mean (SD)	72.7 (8.8)	72.9 (8.2)
Sex		
Men	718 (51.1)	4,366 (50.6)
Women	688 (48.9)	4,264 (49.4)
Duration of asthma/COPD on index date; median (IQR)	12.9 (7.3-20.7)	12.4 (7.2-19.9)
Pulmonary diagnosis type		
Asthma	1,047 (74.5)	6,633 (76.9)
Asthma and COPD	226 (16.1)	1,236 (14.3)
COPD	133 (9.5)	761 (8.8)

Abbreviations: COPD=chronic obstructive pulmonary disease; IQR=interquartile range; PD=Parkinson's disease; SD=standard deviation

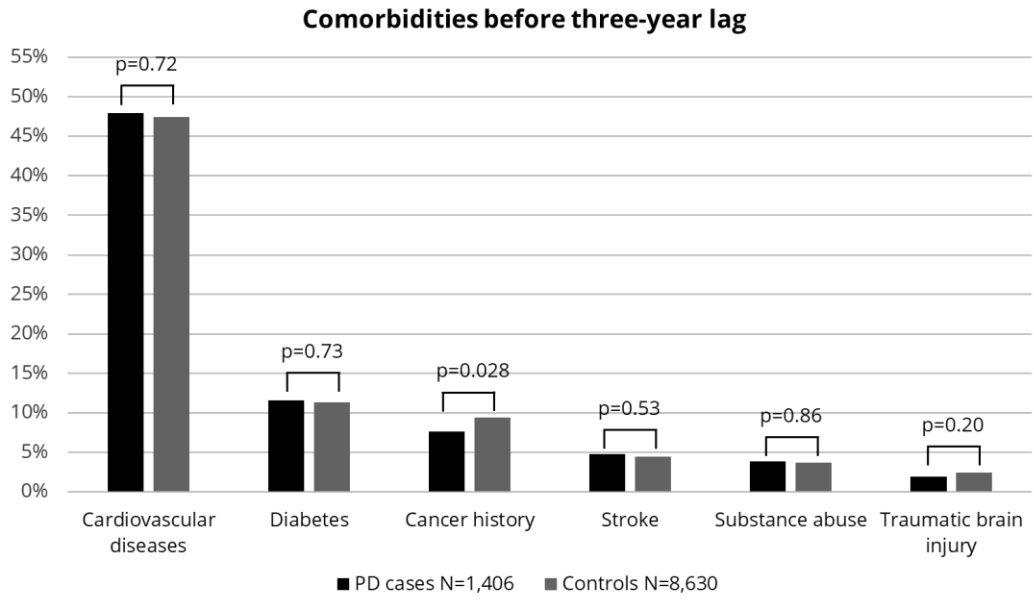


Figure 11. Different covariates between Parkinson's disease (PD) cases and matched controls with asthma/chronic obstructive pulmonary disease.

Over 86% of cases and controls had purchased an β2AR agonist. The most used short-acting β2AR agonist was salbutamol; among long-acting β2AR agonists, it was salmeterol (Figure 12). Only eight controls had purchased indacaterol, and none purchased olodaterol or vilanterol. Use before the 3-year lag of either short- or long-acting β2AR agonists was not associated with PD risk (aOR 1.13; 95% CI 0.95-1.33 and 1.01; 0.89-1.14, respectively). Additional adjustment with use of inhaled anticholinergics and corticosteroids had no effect on the association.

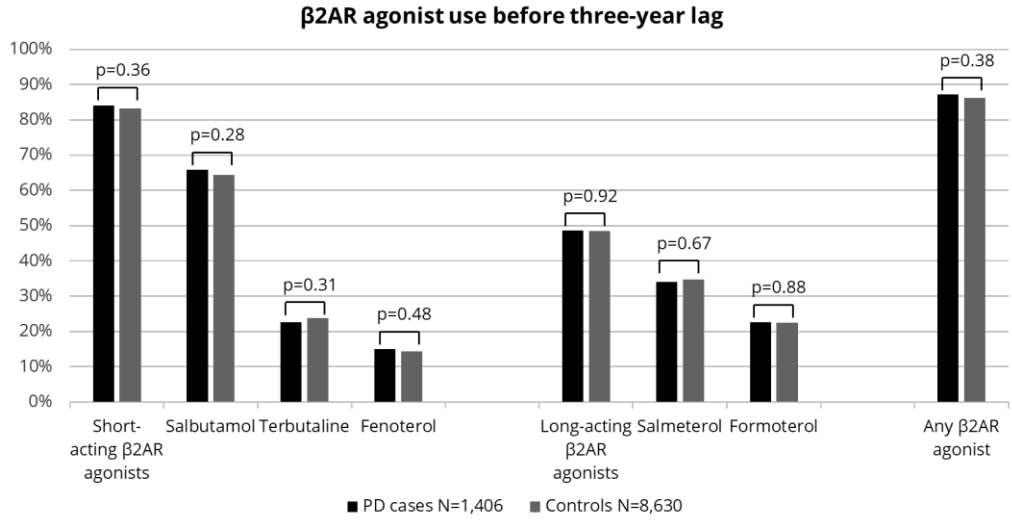


Figure 12. Exposure to β2-adrenoceptor (β2AR) agonists before the 3-year lag among Parkinson's disease (PD) cases and matched controls with asthma/chronic obstructive pulmonary disease.

In dose-response analyses, quartiles of cumulative DDDs for short-, long-acting, or any β2AR agonists were not associated with PD risk (Figure 13). The result was similar in the sensitivity analysis with tertile division; however, the highest tertile of cumulative DDDs for any β2AR agonist (1,275-15,246 DDDs) showed a borderline protective association due to a narrower CI (aOR 0.85; 95% CI 0.72-1.00).

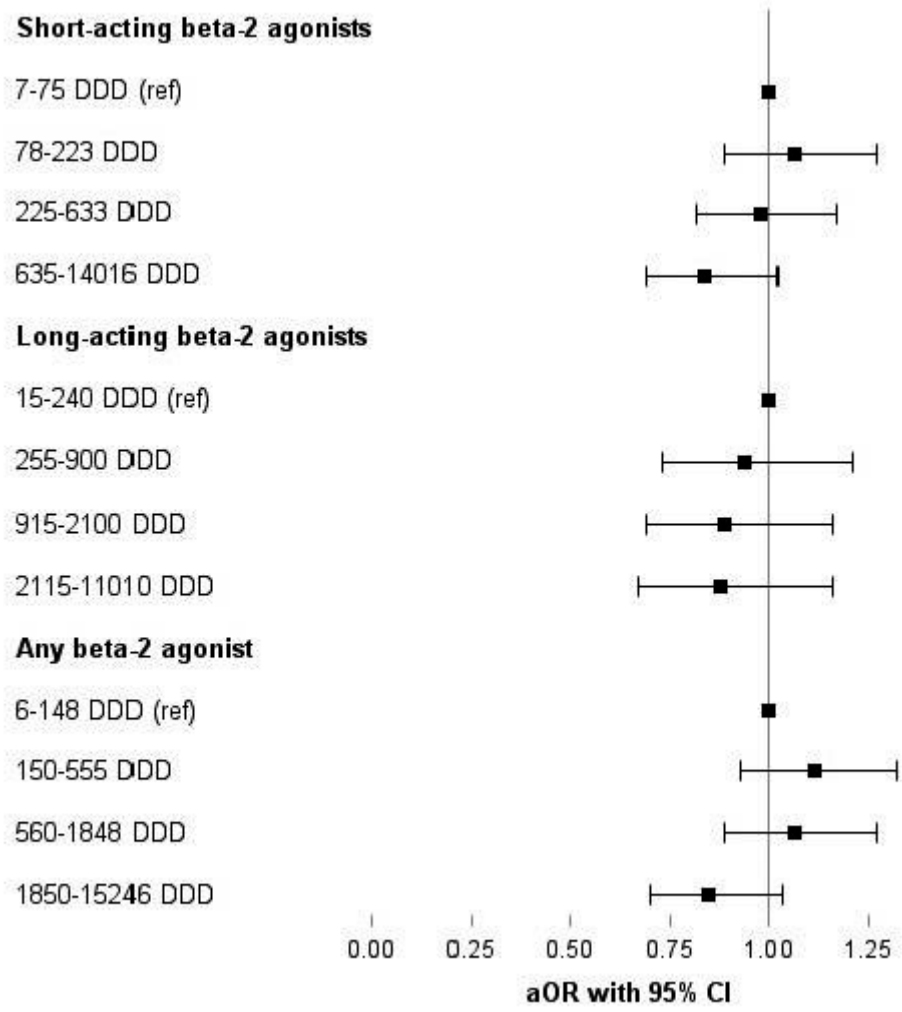


Figure 13. Adjusted odds ratios (aORs) with 95% confidence intervals (CIs) for evaluating the associations between β2AR agonists (beta-2 agonists) and Parkinson's disease risk across the quartiles of cumulative defined daily doses (DDDs).

Different levels of annual exposure to short-acting or any β2AR agonists were not associated with PD risk (Figure 14). The highest quartile of long-acting β2AR agonists (311-1,032 DDD/year) was associated with decreased PD risk (aOR 0.75; 95% CI 0.58-0.97). Correspondingly, in the sensitivity analysis, the association weakened for the highest tertile for annual exposure to long-acting β2AR agonists (280-1,032 DDD/year, aOR 0.82; 95%

CI 0.65-1.02). Tertile categorization showed no dose-response association for annual exposure to short-acting or any β2AR agonists.

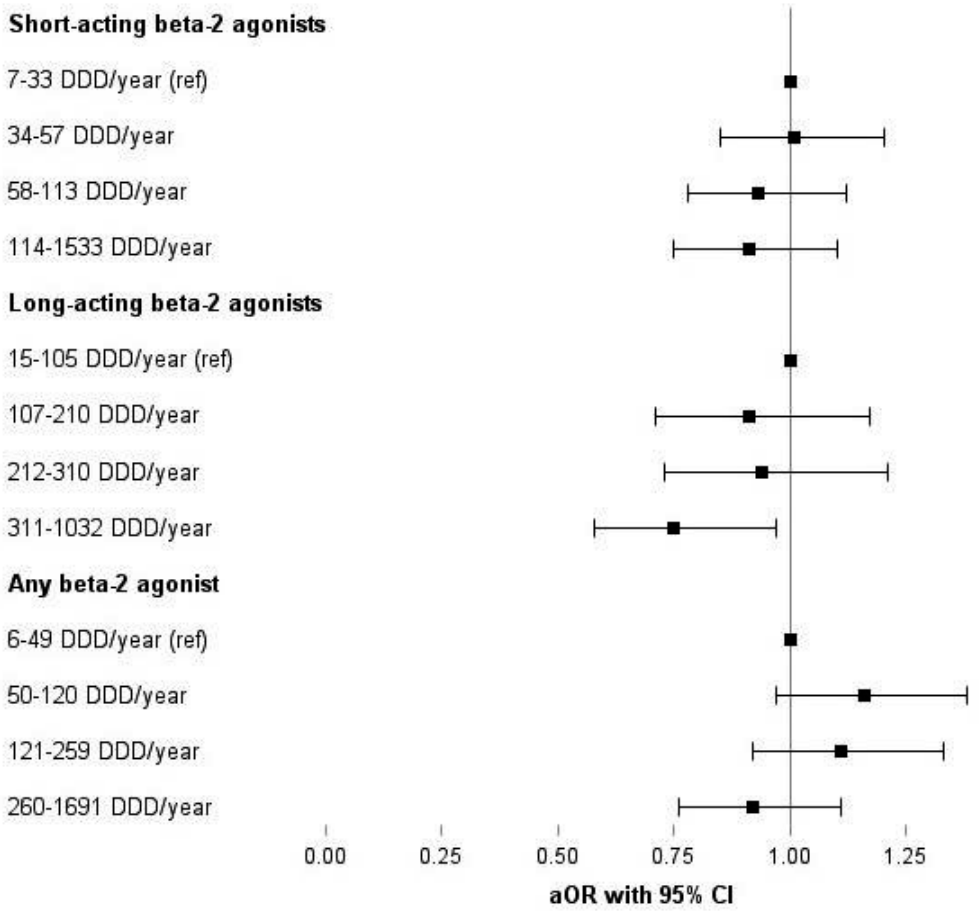


Figure 14. Adjusted odds ratios (aORs) with 95% confidence intervals (CIs) for evaluating associations between β2AR agonists (beta-2 agonists) and Parkinson's disease risk across the quartiles of annual exposure. DDD=defined daily dose

In the analysis for annual exposure to long-acting β2AR agonists stratified by pulmonary diagnosis type, the lowest aORs were for those with both asthma and COPD; the third quartile was associated with decreased PD risk (aOR 0.48; 95% CI 0.27-0.87, Figure 15). For asthma, the

highest quartile was modestly associated with decreased PD risk (aOR 0.74; 95% CI 0.55-1.01). No associations emerged in persons with COPD as CIs were wide (n=130).

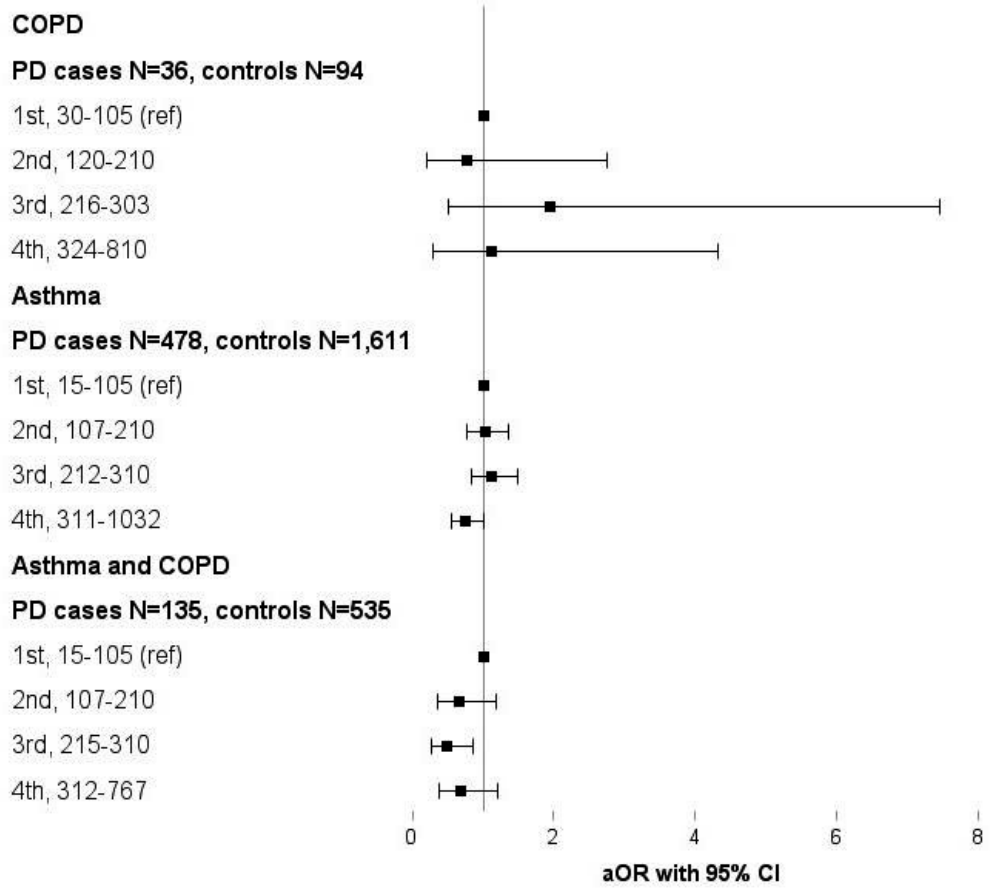


Figure 15. Stratified analysis across the quartiles of average annual exposure to long-acting β2AR agonists by pulmonary diagnosis type. aOR=adjusted odds ratio; CI=confidence interval; COPD=chronic obstructive pulmonary disease

The highest median cumulative DDDs and annual exposure to short-, long-acting, or any β2AR agonists consistently appeared in those with both asthma and COPD diagnoses (Figure 16). Medians differed when compared between the three different pulmonary diagnosis types ($p<0.0001$).

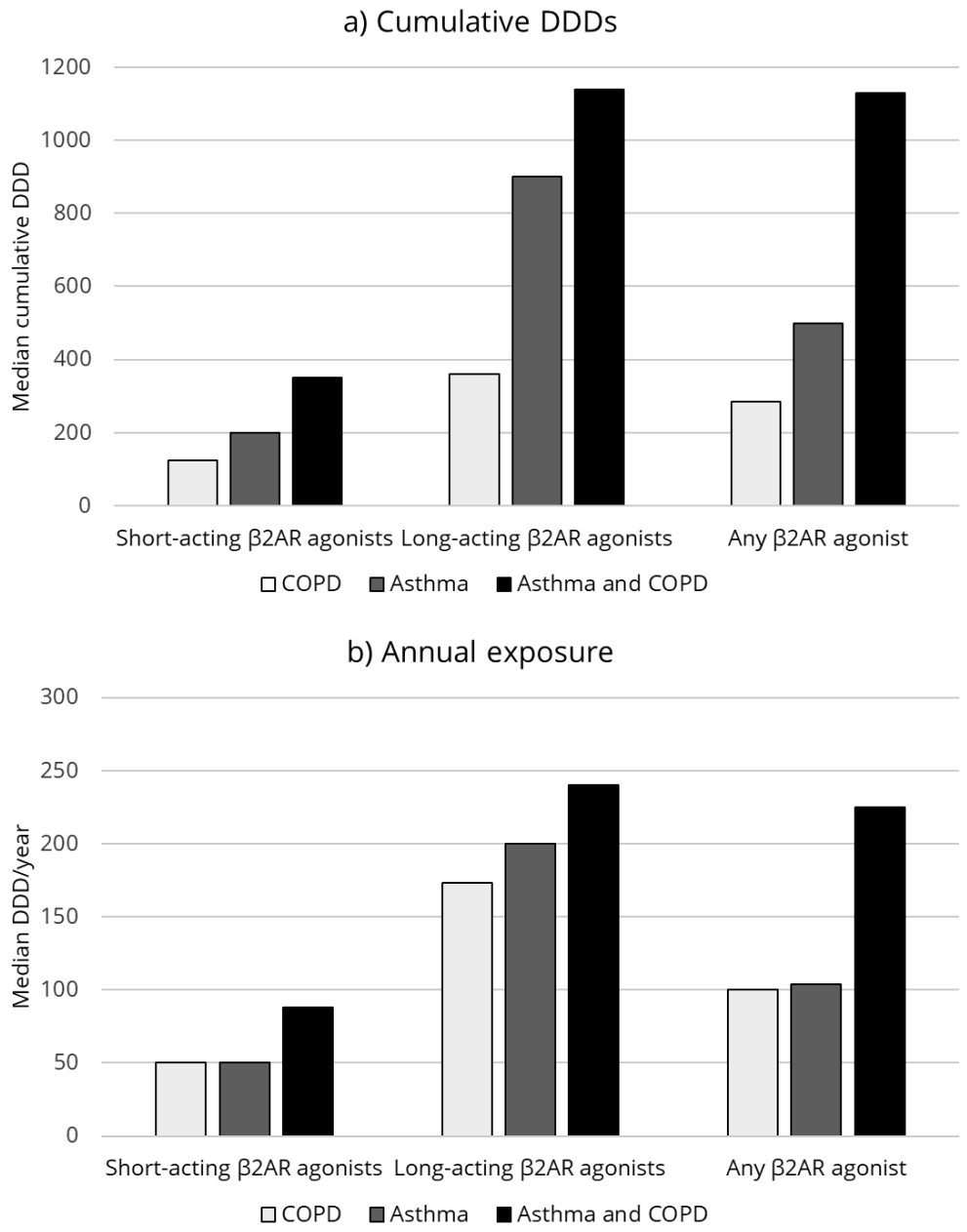


Figure 16. a) Cumulative DDD and b) annual exposure (DDD/year) for β2AR agonists among different pulmonary diagnosis types. P values for all comparisons between different pulmonary diagnosis types were <0.0001. COPD=chronic obstructive pulmonary disease; DDD=defined daily dose

6 DISCUSSION

6.1 INCIDENCE OF MUSCLE RELAXANT USE IN RELATION TO PARKINSON'S DISEASE DIAGNOSIS (STUDY I)

The incidence rate for any muscle relaxant use was constantly higher in persons with PD from three years before PD diagnosis until six months after, in relation to comparison persons. Since no similar previous studies on muscle relaxant use in PD exist, these findings cannot be directly compared. However, muscle relaxant use can reflect occurrence of different prodromal musculoskeletal symptoms. According to previous findings, the prevalence of shoulder or neck pain or stiffness, which can be indirect symptoms of rigidity, was higher in persons with PD even a decade before PD diagnosis (Bohlken et al., 2022; Schrag et al., 2022).

The highest incidence rate for muscle relaxant use was observed in the 6-month interval prior to PD diagnosis, with a 2-fold higher incidence compared with persons without PD. This rate may be explained by general practitioners (GPs) prescribing muscle relaxants to relieve muscle symptoms even in cases when GPs have sent a referral to neurological clinic. Gaining access to neurological specialized health care services after referral can take months and delay the diagnostic process. Muscle relaxant initiations were comparable with persons without PD within a 6-month interval after PD diagnosis, presumably due to dopaminergic therapy initiation, which may have alleviated muscle symptoms.

Better understanding of PD-related muscle symptoms could prevent the use of inappropriate medications as older populations are susceptible to adverse effects of muscle relaxants. Despite the historical use of orphenadrine in PD treatment, it is not recommended in persons ≥65 due to its anticholinergic adverse effects increasing risk of confusion, constipation, and falls (Brocks, 1999; By the 2023 American Geriatrics Society Beers Criteria® Update Expert Panel, 2023). Tizanidine, the most frequently initiated muscle relaxant, is not recommended in persons >75 due to risk of sedation and hypotension among others, according to a

Finnish Med75+ database, which provides recommendations for drug use in older persons (Meds75+, 2023). Baclofen should be used with caution in persons with renal insufficiency, due to increased encephalopathy risk, but the risk of sedation, confusion, and falls also limits its use in older persons (By the 2023 American Geriatrics Society Beers Criteria® Update Expert Panel, 2023; Meds75+, 2023). Baclofen may also worsen PD symptoms in levodopa-treated persons (Lees et al., 1978). Only 1% of users with PD had initiated baclofen during follow-up.

Musculoskeletal symptoms can be an early PD sign and, together with early non-motor symptoms, they may help in identifying persons at risk of developing PD. Identifying these persons would enable conducting trials with disease-modifying interventions in the prodromal stages (Mahlknecht et al., 2022). A better assessment of prodromal symptoms might also lead to earlier diagnosis (Berg et al., 2015)

6.2 DISEASE-MODIFYING ANTIRHEUMATIC DRUGS AND RISK OF PARKINSON'S DISEASE (STUDY II)

DMARD use could explain reduced PD risk in persons with RA (Gonzalez-Latapi and Marras, 2022). Nevertheless, the DMARD-PD relationship has been largely unexplored. Study II showed that different DMARDs or corticosteroids were not associated with PD risk, except for chloroquine/hydroxychloroquine in an indication-restricted study on persons with RA. The result remained with and without a 3-year lag in exposure assessment prior to PD diagnosis.

No previous register-based study has assessed the association between individual DMARDs and PD risk within persons with RA. Instead, DMARD use in persons with RA has been compared with control groups without RA in two cohort studies (Kang et al., 2023; Sung et al., 2016). In Sung et al. (2016), DMARD use, in general, was associated with 36% lower PD risk; among these, biologic DMARDs were associated with 43% lower PD risk. Noteworthily, nonusers with RA had a similar inverse association. On the contrary, in Kang et al. (2023), the use of biologic DMARDs was not associated with PD risk whereas nonusers with RA had 78% increased PD

risk. What further complicates the comparison is that RA itself was inversely associated with PD risk in these studies since Sung et al. reported lower risk while Kang et al. highlighted increased risk. These conflicting findings warrant closer inspection of individual DMARDs while accounting for possible confounding by indication.

Study II demonstrated that chloroquine/hydroxychloroquine was associated with 26% reduced relative PD risk with a 3-year lag period and a somewhat stronger association without the lag. Chloroquine/hydroxychloroquine has been related to reduced PD risk in two previous US case-control studies, but findings are not directly comparable to Study II as those studies were not restricted to persons with RA (Racette et al., 2018; Song et al., 2023). Hydroxychloroquine was associated with 23% reduced relative PD risk when compared to nonusers in Racette et al. (2018). After researchers applied a 1-year lag, this association attenuated. In another study, also based on Medicare claims data, chloroquine/hydroxychloroquine was associated with 16% lower PD risk compared to nonusers with a 1-year lag (Song et al., 2023). Both studies are limited by a short two-year exposure assessment period, which may have led to exposure misclassification. A 1-year lag might be inadequate to account for reverse causality. PD cases have been differently identified between these two studies and FINPARK. In these two, only atypical parkinsonism and dementia with Lewy bodies were accounted for as possible misdiagnoses whereas FINPARK has more extensive exclusion criteria. Despite differences in study population and design, Study II findings support potential reduced PD risk among chloroquine/hydroxychloroquine users.

Chloroquine and hydroxychloroquine were initially used as antimalarial drugs but later proved beneficial in RA and some other autoimmune diseases such as systemic lupus erythematosus (Schrezenmeier and Dörner, 2020). Hydroxychloroquine has replaced chloroquine as it has less adverse effects (Aviña-Zubieta et al., 1998), but chloroquine was still present in our data and was, therefore, included in analyses. Chloroquine and hydroxychloroquine are immunomodulatory drugs with multifaceted mechanisms of action (Schrezenmeier and Dörner, 2020). They accumulate

in lysosomes and interfere with lysosomal activity and autophagy, impairing antigen presentation. These drugs inhibit Toll-like receptor signalling and decrease production of pro-inflammatory cytokines. In addition to these molecular- and cellular-level mechanisms, hydroxychloroquine has cardiovascular protective effects. Chloroquine may improve lipid profile as well as reduce the incidence of diabetes and cardiovascular events in persons with RA (Rempenault et al., 2018). Immunomodulatory and cardiovascular effects may explain the lower PD risk as immune system dysregulation and cardiovascular risk factors are linked with PD (Potashkin et al., 2020; Tan et al., 2020).

Experimental studies have further explored the potential neuroprotective effects of chloroquine/hydroxychloroquine in different PD models. Chloroquine decreased MPTP-induced oxidative stress both *in vitro* and *in vivo* and suppressed pro-inflammatory mediators in the mouse brain and improved behaviour and cognitive impairment in an MPTP-induced PD mouse model (Kartik et al., 2023). Chloroquine improved 6-hydroxydopamine (6-OHDA)-induced neurotoxicity *in vitro* (Kim et al., 2015). Hydroxychloroquine improved motor performance in both rotenone- and 6-OHDA-induced PD rat models (Athari et al., 2022; Hedya et al., 2019). Hydroxychloroquine also reduced α-synuclein protein in the *substantia nigra pars compacta* of rats (Athari et al., 2022).

Methotrexate is an interesting drug in that it is the first-line treatment in RA and long-term pharmacotherapy might lower PD risk (Aletaha and Smolen, 2018; Gonzalez-Latapi and Marras, 2022). Methotrexate reduces inflammation although it is administered only once per week in RA (Swierkot and Szechiński, 2006). Nevertheless, according to previous studies, methotrexate apparently do not lower PD risk. Racette et al. (2018) reported 16% lower PD risk when exposure was measured up to PD diagnosis and compared to nonusers; however, with a 1-year lag, the association attenuated. Methotrexate was not significantly associated with PD risk with a 1-year lag in a case-control study by Song et al. (2023). In our Study II, no association was observed between methotrexate use and PD risk with or without a 3-year lag in persons with RA.

Regarding other individual DMARDs, knowledge of their relationship with PD risk is lacking. Sulfasalazine, which is included in triple therapy along with methotrexate and hydroxychloroquine, is a common RA drug (Möttönen et al., 1999). No association was found in Racette et al. (2018) nor in Study II. Azathioprine, leflunomide, and mycophenolate were associated with lower PD risk; however, this association disappeared after they applied a 1-year lag (Racette et al., 2018). In Study II, these drugs, along with different biologic DMARDs, were classified as immunosuppressants, which were not associated with PD risk. Biologic DMARDs are relatively new drugs, and their use was infrequent during the years of available data. Biologic and targeted synthetic DMARDs have specific targets in the immune system pathway and are more powerful immunosuppressants than traditional synthetic DMARDs (Aletaha and Smolen, 2018). Therefore, their relationship with PD risk is interesting. As a comparison, TNF-α inhibitors were associated with reduced PD incidence in persons with inflammatory bowel disease compared to unexposed persons (Peter et al., 2018).

Pharmacoepidemiological studies of specific DMARDs are complicated by the fact that DMARDs are often used in combination therapy in RA and that each DMARD has a specific mechanism of action. Drug choice is dependent on symptom severity and tolerance (Smolen et al., 2020), which may confound the association if these features influence PD risk. We accounted for combination treatments by observing which types of DMARDs persons were exposed to before the start of the 3-year lag. Sulfasalazine monotherapy was the most common category to which other exposure histories were compared, but no associations emerged, which may be due to lack of statistical power as only a few persons had certain combinations. An active comparator instead of nonuse was used to reduce potential confounding by disease severity (Stürmer et al., 2020). PD cases and controls were also matched for RA duration, and a sensitivity analysis with additional adjustment for disease duration had no effect on results.

6.3 B2AR AGONISTS AND RISK OF PARKINSON'S DISEASE (STUDY III)

In Study III, which was restricted to persons with asthma/COPD, inhaled β2AR agonists were not associated with PD risk. Possible reverse causality was addressed by applying a 3-year lag in exposure assessment. Addressing confounding by indication and smoking are typical challenges in epidemiological studies on β2AR agonists and PD risk, and such confounding may have contributed to lower PD risk in previous studies (Hopfner et al., 2019; Searles Nielsen et al., 2018). The main indications for β2AR agonists are asthma and COPD, which are also associated with an increased risk of PD development (Cheng et al., 2015; C.-H. Li et al., 2015). These pulmonary diseases are affected by smoking as it is the greatest COPD risk factor, (GOLD, 2023) increasing the risk of adult-onset asthma and worsening asthma control (Jaakkola et al., 2019). Smoking is difficult to capture by using routinely collected health care data since it is not directly recorded in registers in Finland or in other countries (Chen et al., 2020; Liu et al., 2023; Tuominen et al., 2023). Indication-restriction may control the issue by reducing the heterogeneity of smoking history in the study population; however, it is probably still differently distributed between persons with COPD and asthma.

Study III findings are in line with those from a previous nested case-control study, in which the use of any β2AR agonist was not associated with PD risk when compared to nonuse among persons with COPD (Chen et al., 2020). Different purchase frequencies within a 2-year exposure assessment period or the length of the lag from 2 to 3 years had no influence on the result. Their data lacked information on smoking. However, restriction to persons with COPD can eliminate variation in smoking, which may no longer confound the association.

On the contrary, two other indication-restricted studies found a modest negative association between β2AR agonists and PD risk. In a nested case-control study of persons with asthma/COPD, each additional month of exposure to short-acting β2AR agonists was associated with 10% lower PD risk (Marras et al., 2020). In a cohort study of persons with asthma/COPD

(including bronchiectasis), the number of 30-day claims for any β2AR agonist during a 4-year period was modestly associated with lower PD risk (OR 0.986; 95% CI 0.977-0.995) (Nadeem et al., 2022). However, these ORs are very close to 1, and no difference emerged in 4-year incidence between users and nonusers of β2AR agonists. Differences in exposure measurement prevent direct comparison to Study III.

Investigation of the dose-response relationship elaborates the link between β2AR agonists and PD risk. When exposure was categorized into quartiles of cumulative DDDs and average annual exposure (DDD/year), no clear dose-response relationship emerged among users. Quartiles of cumulative DDDs for any β2AR agonist regardless of the duration of action were not associated with PD risk. As for annual exposure, the highest quartile of long-acting β2AR agonists was associated with 25% lower PD risk; relative risk estimates for short- or any β2AR agonists did not reach statistical significance.

None of the previous indication-restricted studies calculated cumulative exposure using DDDs. However, two recent Nordic cohort studies of the general population calculated cumulative DDDs across the exposure period (Liu et al., 2023; Tuominen et al., 2023). They included combinations with inhaled anticholinergics and corticosteroids, similar to Study III. When average DDDs for a 2-year exposure period were divided into low and high doses, when compared to nonuse, short- or long-acting β2AR agonists exhibited no dose-response relationship (Liu et al., 2023). Analyses were adjusted for COPD as proxy for smoking. On the contrary, Tuominen et al. (2023) reported a dose-dependent reduced risk across all exposure quantiles for any, short-, long-, and ultra-long-acting β2AR agonists, when compared to nonuse. An exception was the highest quantile for ultra-long-acting β2AR agonists, which was non-significantly associated. After excluding persons with COPD, exposure quantiles for any β2AR agonists were no longer associated with PD risk. Neither of these studies provided exact DDDs, preventing the comparison of cumulative exposure levels with Study III.

Pulmonary disease type modified the association of annual exposure to long-acting β2AR agonists. In the stratified analysis, the lowest point

estimates were among persons with both asthma and COPD. Cumulative exposure in these persons was the highest compared to groups with COPD or asthma alone, which probably reflects disease severity: to manage exacerbations, more frequent use and higher doses are needed (GINA, 2022; GOLD, 2023). Persons with asthma–COPD overlap syndrome reportedly have a higher risk of PD development (Yeh et al., 2018), and they have more symptoms than persons with asthma or COPD alone do (Nielsen et al., 2015). Based on this report, the reason higher β2AR agonist exposure would be beneficial in terms of PD in a group with both asthma and COPD is unclear. This group with both asthma and COPD presumably includes non-smokers; asthma in non-smokers may develop into COPD (Silva et al., 2004). Differential smoking history among β2AR agonist users can confound the association as smokers may require more frequent use and higher doses of β2AR agonists.

As for persons with asthma or COPD alone, the highest quartile of annual exposure to long-acting β2AR agonists had a borderline association with reduced PD risk in asthma, and no associations emerged in persons with COPD. Differential distribution of smoking history among persons with asthma could contribute to lower PD risk suggested in the highest exposure group. COPD findings should be interpreted with caution as the number of persons with only COPD was small, resulting in wide CIs. Nevertheless, relative risk estimates were not suggestive of reduced PD risk, in line with those in Chen et al. (2020). Despite the experimental findings on potential effects on α-synuclein pathology and immunomodulatory functions (Magistrelli and Comi, 2020), in the light of Study III and previous epidemiological literature, β2AR agonists do not seem to modify PD risk in persons with pulmonary disease.

6.4 METHODOLOGICAL CONSIDERATIONS

A particular strength of this thesis is the large nationwide study population. Persons with PD were identified from the Special Reimbursement Register, based on entitlement for reimbursement for PD drugs provided that ICD-code G20 was recorded in connection with classification code 110. The

benefit of this approach is that persons are examined by neurologists who submit statements to the SII, which centrally reviews whether strict eligibility criteria are met. Despite a record of PD diagnosis, comprehensive exclusion criteria based on neurologist expertise were applied in FINPARK to account for possible misdiagnoses as diagnosing PD is challenging, especially in the early stage (Adler et al., 2021). FINPARK exclusion criteria are not validated, but the proportion of excluded persons (roughly 1/4) is similar to that of incorrect diagnoses by general neurologists in Finland (Joutsa et al., 2014). One limitation is that the starting point of the diagnostic process is not recorded in registers; thus, the date of entitlement for reimbursement is an estimate of diagnosis time.

Register-based Finnish data on drug and health care use provides an extensive source for pharmacoepidemiological research. One strength is that all citizens are covered by publicly financed health care, which is not limited by residential area or socioeconomic position, yielding nationally representative findings (Laugesen et al., 2021). Furthermore, health registers have a long history in Finland (Gissler and Haukka, 2004), enabling a long follow-up before PD diagnosis. The validity of the Prescription Register is high and suitable for risk factor studies as it is free from recall bias (Laugesen et al., 2021). Observation gaps in drug exposure are possible due to hospital stays or gaps in reimbursement periods. Over-the-counter drugs are not included, but all drugs studied in this thesis are only available with a prescription.

Study I was the first to describe muscle relaxant use as a proxy for muscle symptoms in prodromal PD. Analyses were restricted to new users to avoid prevalent user bias (Ray, 2003) since prevalent use may not capture the relationship with PD-associated symptoms. The rationale for the 4-year follow-up preceding PD diagnosis is based on the available data in the Prescription Register since 1995. Data restriction to those diagnosed with PD from 2000 onwards ensured that all persons included had at least 5 years of purchase data prior to PD without excessive reduction of sample size in FINPARK. The Prescription Register does not capture drug use in hospitals or in public nursing homes; therefore, to reduce potential

misclassification of exposure, the follow-up was censored at the beginning of ≥90 days of hospitalization.

The long history of register data permitted us to control for potential reverse causality in Studies II and III and yet have a relatively long exposure assessment period. Lag length was chosen based on Study I findings. The appearance of disturbing motor-related symptoms in the FINPARK cohort 3 years before diagnosis reflects neurodegeneration impact. Despite neurodegeneration beginning long before diagnosis (Berg et al., 2021), half of the dopaminergic cells may still be functional in the *substantia nigra pars compacta* at the time when motor symptoms meet diagnostic criteria (Cheng et al., 2010). Thus, in theory, drug exposure before the 3-year lag could still modify neurodegeneration to some extent. Additionally, to prevent DMARDs or β2AR agonists from being prescribed or avoided due to prodromal symptoms or a result of increased health care contact due to diagnostic PD processes, measuring exposure before the occurrence of disturbing motor-related symptoms was important. RA, asthma, and COPD are chronic diseases and may also influence PD identification due to more regular health care visits.

To trace the earliest time of diagnosis and to identify all persons with RA and asthma/COPD in the indication-restricted Studies II and III, a comprehensive attempt was conducted by using both the Care Register for Health Care and the Special Reimbursement Register. The Care Register for Health Care has good accuracy for common diagnoses and covers persons with hospital visits and, nowadays, also specialist outpatient visits (Sund, 2012). The use of the Special Reimbursement Register with an ICD code record, indicating the condition for which the reimbursement was granted, gives complementary information as it captures outpatient care in both public and private sectors. In addition, rheumatologists issue RA statements while mainly GPs do those for asthma/COPD. In all cases, diagnosis statement fulfilment is checked by medical doctors at the SII.

The inclusion criteria, including the specific diagnosis codes in indication-restricted designs, were based on clinical experience in rheumatology and pulmonary diseases. Different ICD versions have been used during the years, and disease classification precision has evolved

through ICD revisions, which pose a potential limitation (Smedby and Schiøler, 2006). The focus in Study II was to identify seropositive RA because seronegative RA is a different disease entity and is linked with diagnostic inaccuracies (Paalanen et al., 2019). Tracing the earliest diagnosis was challenging, as the 8th revision makes no distinction based on serology. To reduce potential differential misclassification, the impact of changes in diagnostic processes was minimized by using not just ICD-8 codes to detect RA. Furthermore, due to imprecise coding accuracies (3 to 5 characters) in the Special Reimbursement Register, the study population can include some persons with the seronegative disease type. In Study III, misclassification of asthma and COPD is theoretically possible since asthma can be difficult to differentiate from COPD, especially in older persons (Bouwens et al., 2022). COPD is universally underdiagnosed, including in Finland (Kainu et al., 2013).

The indication-restriction design reduces heterogeneity in possible confounders; this reduction is seen in the similar distribution of comorbid conditions in Studies II and III. Despite indication-restriction, residual confounding by disease severity may remain (Salas et al., 1999) because treatment choice and prescribed doses depend on disease stage. To control possible differential association with PD by disease severity, controls were matched with PD case by disease duration and, in Study III, additionally by pulmonary diagnosis type. Nonusers may be intrinsically different from users in terms of disease severity. Apart from comparing use to nonuse, an active comparator was used in Study II in an additional analysis of exposure histories; in Study III, dose-response analyses were conducted among users.

A general limitation of register-based data is the lack of information on lifestyle factors, particularly smoking. This thesis included mental and behavioural disorders due to tobacco use (ICD-10 F17) in the substance abuse variable, but this code is unlikely to identify many smokers. Several studies demonstrate that smokers are less likely to develop PD (Hernán et al., 2002). Smoking could theoretically confound the association between DMARDs and PD risk since smoking increases RA risk (Sugiyama et al.,

2010). Smoking probably more profoundly affects the relationship between β2AR agonists and PD risk, as discussed above.

The Prescription Register contains information on dosage via DDDs, which was used to determine dose-response relationship in Study III, but its limitations should be acknowledged. DDDs are good for comparing rough consumption but, since one DDD is the assumed average maintenance dose per day in adults, it is not necessarily the prescribed dose or the dose used (WHOCC - Definition and general considerations, 2022). As an example, one DDD for salbutamol is 0.8 mg; as it is often used as needed for symptom relief, all persons with salbutamol purchases taking one DDD daily is unlikely (WHOCC - ATC/DDD Index, 2023). Unit doses are assigned for combination products of β2AR agonists, which may not be equivalent to DDDs of the single active ingredient (WHO Collaborating Centre for Drug Statistics Methodology, 2023). As an example, one DDD of formoterol in a combination product (ATC R03AK07) contains 2-4 unit doses corresponding to 18 µg formoterol and 320-640 µg budesonide while one DDD for formoterol is 24 µg; for inhaled budesonide, it is 800-1500 µg (WHOCC - ATC/DDD Index, 2023; WHOCC - List of DDDs combined products, 2023). Combination treatment is, however, very common in both asthma and COPD (GINA, 2022; GOLD, 2023); therefore, including them in the calculation of cumulative exposure is justifiable. Additionally, DDDs in combination products (ATC R03AK) are based on maintenance treatment of severe asthma and COPD and not on solely one of them (WHO Collaborating Centre for Drug Statistics Methodology, 2023). This fact is relevant as Study III included both pulmonary diseases.

A limitation of both the indication-restriction and lag period approach is sample size reduction, which may decrease power and precision by limiting the detection of weak associations and increasing confidence interval width. The findings especially for biologic DMARDs and conclusions from stratified analyses in Study III should be interpreted with caution as the small number of the exposed may affect effect estimates. In Studies II and III, controls were rematched using comparison persons from the entire FINPARK study. The ideal approach would have been to re-retrieve controls

from the national registers so that all persons in Finland with RA in Study II or asthma/COPD in Study III would have been the actual source population for control selection. This approach would have led to a larger number of controls. However, the increased statistical power may not have changed the conclusions. The ideal identification of controls was unfeasible; the selection of controls with RA or asthma/COPD in FINPARK was probably random, yielding, in Studies II and III, estimates that were probably not biased.

7 CONCLUSIONS

Based on the results of this thesis, the following conclusions can be drawn:

1. The incidence of muscle relaxant use was higher in persons with PD already three years before PD diagnosis in relation to comparison persons; this higher incidence may reflect prodromal motor symptoms.

2. Identifying an appropriate exposure assessment period is important when studying risk factors for a disease with a long prodromal period such as PD. Drug utilization studies provide information for designing better pharmacoepidemiological risk factor studies.

3. In general, DMARDs were not associated with PD risk in persons with RA. An exception was chloroquine/hydroxychloroquine, which was associated with reduced PD risk.

4. Any use of either short-acting or long-acting β2AR agonists was not associated with PD risk when compared to nonuse in persons with asthma/COPD.

5. In dose-response analysis, the highest quartile of annual exposure to long-acting β2AR agonists was associated with reduced PD risk, but this association was modified by pulmonary disease type. The lowest risk estimates were in persons with both asthma and COPD, which may be explained by residual confounding of disease severity and smoking.

7.1 IMPLICATIONS FOR CLINICAL PRACTICE AND FUTURE RESEARCH

1. Nonspecific muscle symptoms seem to be present in prodromal PD. Older adults experiencing muscle symptoms should be examined thoroughly to avoid unnecessary use of muscle relaxants in a population susceptible to their adverse effects.

2. In pharmacoepidemiological risk factor studies, it is important to consider appropriate exposure assessment period, confounding by indication, and investigation of dose-response relationship.

3. Further epidemiological and experimental studies are needed to explain the association between chloroquine/hydroxychloroquine and reduced PD risk.

4. Future studies should investigate how biologic DMARDs and targeted synthetic DMARDs are associated with PD risk.

5. Future studies on inhaled β2AR agonists and PD risk should have validated and comprehensive information on smoking history.

REFERENCES

Abosamak, N.R., Shahin, M.H., 2023. Beta 2 Receptor Agonists/Antagonists., in: StatPearls. StatPearls Publishing, Treasure Island (FL).

Adler, C.H., Beach, T.G., Zhang, N., Shill, H.A., Driver-Dunckley, E., Mehta, S.H., Atri, A., Caviness, J.N., Serrano, G., Shprecher, D.R., Sue, L.I., Belden, C.M., 2021. Clinical Diagnostic Accuracy of Early/Advanced Parkinson Disease: An Updated Clinicopathologic Study. Neurol Clin Pract 11, e414–e421. https://doi.org/10.1212/CPJ.0000000000001016

Ahlskog, J.E., Muenter, M.D., 2001. Frequency of levodopa-related dyskinesias and motor fluctuations as estimated from the cumulative literature. Mov Disord 16, 448–458. https://doi.org/10.1002/mds.1090

Alamanos, Y., Voulgari, P.V., Drosos, A.A., 2006. Incidence and prevalence of rheumatoid arthritis, based on the 1987 American College of Rheumatology criteria: a systematic review. Semin Arthritis Rheum 36, 182–188. https://doi.org/10.1016/j.semarthrit.2006.08.006

Aletaha, D., Neogi, T., Silman, A.J., Funovits, J., Felson, D.T., Bingham, C.O. 3rd, Birnbaum, N.S., Burmester, G.R., Bykerk, V.P., Cohen, M.D., Combe, B., Costenbader, K.H., Dougados, M., Emery, P., Ferraccioli, G., Hazes, J.M.W., Hobbs, K., Huizinga, T.W.J., Kavanaugh, A., Kay, J., Kvien, T.K., Laing, T., Mease, P., Ménard, H.A., Moreland, L.W., Naden, R.L., Pincus, T., Smolen, J.S., Stanislawska-Biernat, E., Symmons, D., Tak, P.P., Upchurch, K.S., Vencovský, J., Wolfe, F., Hawker, G., 2010. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum 62, 2569–2581. https://doi.org/10.1002/art.27584

Aletaha, D., Smolen, J.S., 2018. Diagnosis and Management of Rheumatoid Arthritis: A Review. JAMA 320, 1360–1372. https://doi.org/10.1001/jama.2018.13103

Angot, E., Steiner, J.A., Hansen, C., Li, J.-Y., Brundin, P., 2010. Are synucleinopathies prion-like disorders? Lancet Neurol 9, 1128–1138. https://doi.org/10.1016/S1474-4422(10)70213-1

Antonini, A., Tinazzi, M., Abbruzzese, G., Berardelli, A., Chaudhuri, K.R., Defazio, G., Ferreira, J., Martinez-Martin, P., Trenkwalder, C., Rascol,

O., 2018. Pain in Parkinson's disease: facts and uncertainties. Eur J Neurol 25, 917-e69. https://doi.org/10.1111/ene.13624
Anttila, M., Hartikainen, S., Herukka, S.-K., Kaasinen, V., Tolppanen, A.-M., 2020. Parkinsonin taudin lääkkeiden erityiskorvausoikeuden saajien määrän muutos vuosina 1996–2015. Suomen Lääkärilehti 75, 2297–2302.
Arfè, A., Corrao, G., 2015. Tutorial: strategies addressing detection bias were reviewed and implemented for investigating the statins-diabetes association. J Clin Epidemiol 68, 480–488. https://doi.org/10.1016/j.jclinepi.2014.12.001
Armstrong, M.J., Okun, M.S., 2020. Diagnosis and Treatment of Parkinson Disease: A Review. JAMA 323, 548–560. https://doi.org/10.1001/jama.2019.22360
Arnett, F.C., Edworthy, S.M., Bloch, D.A., McShane, D.J., Fries, J.F., Cooper, N.S., Healey, L.A., Kaplan, S.R., Liang, M.H., Luthra, H.S., 1988. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 31, 315–324. https://doi.org/10.1002/art.1780310302
Artusi, C.A., Sarro, L., Imbalzano, G., Fabbri, M., Lopiano, L., 2021. Safety and efficacy of tolcapone in Parkinson's disease: systematic review. Eur J Clin Pharmacol 77, 817–829. https://doi.org/10.1007/s00228-020-03081-x
Ascherio, A., Schwarzschild, M.A., 2016. The epidemiology of Parkinson's disease: risk factors and prevention. Lancet Neurol 15, 1257–1272. https://doi.org/10.1016/S1474-4422(16)30230-7
Athari, S.Z., Farajdokht, F., Sadigh-Eteghad, S., Mohajeri, D., Nourazar, M.A., Mohaddes, G., 2022. Hydroxychloroquine attenuated motor impairment and oxidative stress in a rat 6-hydroxydopamine model of Parkinson's disease. Int J Neurosci 1–10. https://doi.org/10.1080/00207454.2022.2074848
Aviña-Zubieta, J.A., Galindo-Rodriguez, G., Newman, S., Suarez-Almazor, M.E., Russell, A.S., 1998. Long-term effectiveness of antimalarial drugs in rheumatic diseases. Ann Rheum Dis 57, 582–587. https://doi.org/10.1136/ard.57.10.582
Bacelis, J., Compagno, M., George, S., Pospisilik, A., Brundin, P., Naluai, Å., Brundin, L., 2021. Decreased Risk of Parkinson's Disease After Rheumatoid Arthritis Diagnosis: A Nested Case-Control Study with Matched Cases and Controls. J.Parkinsons Dis. https://doi.org/10.3233/JPD-202418

Barnes, P.J., 2008. Immunology of asthma and chronic obstructive pulmonary disease. Nat Rev Immunol 8, 183–192. https://doi.org/10.1038/nri2254

Belvisi, D., Pellicciari, R., Fabbrini, G., Tinazzi, M., Berardelli, A., Defazio, G., 2020. Modifiable risk and protective factors in disease development, progression and clinical subtypes of Parkinson's disease: What do prospective studies suggest? Neurobiol.Dis. 134, 104671.

Berg, D., Borghammer, P., Fereshtehnejad, S.-M., Heinzel, S., Horsager, J., Schaeffer, E., Postuma, R.B., 2021. Prodromal Parkinson disease subtypes - key to understanding heterogeneity. Nat Rev Neurol 17, 349–361. https://doi.org/10.1038/s41582-021-00486-9

Berg, D., Postuma, R.B., Adler, C.H., Bloem, B.R., Chan, P., Dubois, B., Gasser, T., Goetz, C.G., Halliday, G., Joseph, L., Lang, A.E., Liepelt-Scarfone, I., Litvan, I., Marek, K., Obeso, J., Oertel, W., Olanow, C.W., Poewe, W., Stern, M., Deuschl, G., 2015. MDS research criteria for prodromal Parkinson's disease. Mov.Disord. 30, 1600–1611. https://doi.org/10.1002/mds.26431

Billingsley, K.J., Bandres-Ciga, S., Saez-Atienzar, S., Singleton, A.B., 2018. Genetic risk factors in Parkinson's disease. Cell Tissue Res 373, 9–20. https://doi.org/10.1007/s00441-018-2817-y

Bjornevik, K., Schwarzschild, M.A., Ascherio, A., 2020. Big health data and Parkinson's disease epidemiology: Challenges and opportunities. Parkinsonism Relat Disord 71, 58–59. https://doi.org/10.1016/j.parkreldis.2020.01.001

Blauwendraat, C., Nalls, M.A., Singleton, A.B., 2020. The genetic architecture of Parkinson's disease. Lancet Neurol 19, 170–178. https://doi.org/10.1016/S1474-4422(19)30287-X

Bloem, B.R., Okun, M.S., Klein, C., 2021. Parkinson's disease. Lancet 397, 2284–2303. https://doi.org/10.1016/S0140-6736(21)00218-X

Bohlken, J., Schrag, A., Riedel-Heller, S., Kostev, K., 2022. Identification of Prodromal Presentations of Parkinson's Disease among Primary Care Outpatients in Germany. Neuroepidemiology 56, 41–49. https://doi.org/10.1159/000520574

Borghammer, P., 2021. The α-Synuclein Origin and Connectome Model (SOC Model) of Parkinson's Disease: Explaining Motor Asymmetry, Non-Motor Phenotypes, and Cognitive Decline. J Parkinsons Dis 11, 455–474. https://doi.org/10.3233/JPD-202481

Bouwens, J.D.M., Bischoff, E.W.M.A., In 't Veen, J.C.C.M., Schermer, T.R., 2022. Diagnostic differentiation between asthma and COPD in

primary care using lung function testing. NPJ Prim Care Respir Med 32, 32. https://doi.org/10.1038/s41533-022-00298-4
Bower, J.H., Maraganore, D.M., Peterson, B.J., Ahlskog, J.E., Rocca, W.A., 2006. Immunologic diseases, anti-inflammatory drugs, and Parkinson disease: a case-control study. Neurology 67, 494–496. https://doi.org/10.1212/01.wnl.0000227906.99570.cc
Braak, H., Ghebremedhin, E., Rub, U., Bratzke, H., Del Tredici, K., 2004. Stages in the development of Parkinson's disease-related pathology. Cell Tissue Res. 318, 121–134. https://doi.org/10.1007/s00441-004-0956-9
Brocks, D.R., 1999. Anticholinergic drugs used in Parkinson's disease: An overlooked class of drugs from a pharmacokinetic perspective. J.Pharm.Pharm.Sci. 2, 39–46.
Burke, R.E., Dauer, W.T., Vonsattel, J.P., 2008. A critical evaluation of the Braak staging scheme for Parkinson's disease. Ann.Neurol. 64, 485–491. https://doi.org/10.1002/ana.21541
Burkes, R.M., Panos, R.J., 2020. Ultra Long-Acting β-Agonists in Chronic Obstructive Pulmonary Disease. J Exp Pharmacol 12, 589–602. https://doi.org/10.2147/JEP.S259328
Burré, J., 2015. The Synaptic Function of α-Synuclein. JPD 5, 699–713. https://doi.org/10.3233/JPD-150642
By the 2023 American Geriatrics Society Beers Criteria® Update Expert Panel, 2023. American Geriatrics Society 2023 updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. J Am Geriatr Soc. https://doi.org/10.1111/jgs.18372
Bykov, K., Yoshida, K., Weisskopf, M.G., Gagne, J.J., 2017. Confounding of the association between statins and Parkinson disease: systematic review and meta-analysis: Statins and Parkinson Disease: Systematic Review and Meta-Analysis. Pharmacoepidemiol Drug Saf 26, 294–300. https://doi.org/10.1002/pds.4079
Camacho-Soto, A., Warden, M.N., Searles Nielsen, S., Salter, A., Brody, D.L., Prather, H., Racette, B.A., 2017. Traumatic brain injury in the prodromal period of Parkinson's disease: A large epidemiological study using medicare data: TBI in the Prodromal Period of PD. Ann Neurol. 82, 744–754. https://doi.org/10.1002/ana.25074
Caslake, R., Moore, J.N., Gordon, J.C., Harris, C.E., Counsell, C., 2008. Changes in diagnosis with follow-up in an incident cohort of patients with parkinsonism. J Neurol Neurosurg Psychiatry 79, 1202–1207. https://doi.org/10.1136/jnnp.2008.144501

Cepeda, M.S., Kern, D.M., Seabrook, G.R., Lovestone, S., 2019. Comprehensive Real-World Assessment of Marketed Medications to Guide Parkinson's Drug Discovery. Clin Drug Investig 39, 1067–1075. https://doi.org/10.1007/s40261-019-00830-4

Cerri, S., Mus, L., Blandini, F., 2019. Parkinson's Disease in Women and Men: What's the Difference? J.Parkinsons Dis. 9, 501–515. https://doi.org/10.3233/JPD-191683

Chang, C.C., Lin, T.M., Chang, Y.S., Chen, W.S., Sheu, J.J., Chen, Y.H., Chen, J.H., 2018. Autoimmune rheumatic diseases and the risk of Parkinson disease: a nationwide population-based cohort study in Taiwan. Ann.Med. 50, 83–90. https://doi.org/10.1080/07853890.2017.1412088

Chapman, D.G., Irvin, C.G., 2015. Mechanisms of airway hyper-responsiveness in asthma: the past, present and yet to come. Clin Exp Allergy 45, 706–719. https://doi.org/10.1111/cea.12506

Chaudhuri, K.R., Schapira, A.H.V., 2009. Non-motor symptoms of Parkinson's disease: dopaminergic pathophysiology and treatment. Lancet Neurol 8, 464–474. https://doi.org/10.1016/S1474-4422(09)70068-7

Chen, H., 2018. The Changing Landscape of Parkinson Epidemiologic Research. J Parkinsons Dis 8, 1–12. https://doi.org/10.3233/JPD-171238

Chen, H., Huang, X., Guo, X., Mailman, R.B., Park, Y., Kamel, F., Umbach, D.M., Xu, Q., Hollenbeck, A., Schatzkin, A., Blair, A., 2010. Smoking duration, intensity, and risk of Parkinson disease. Neurology 74, 878–884. https://doi.org/10.1212/WNL.0b013e3181d55f38

Chen, W., Sadatsafavi, M., Tavakoli, H., Samii, A., Etminan, M., 2020. Effects of β2-Adrenergic Agonists on Risk of Parkinson's Disease in COPD: A Population-Based Study. Pharmacotherapy 40, 408–415. https://doi.org/10.1002/phar.2383

Cheng, C.M., Wu, Y.H., Tsai, S.J., Bai, Y.M., Hsu, J.W., Huang, K.L., Su, T.P., Li, C.T., Tsai, C.F., Yang, A.C., Lin, W.C., Pan, T.L., Chang, W.H., Chen, T.J., Chen, M.H., 2015. Risk of developing Parkinson's disease among patients with asthma: a nationwide longitudinal study. Allergy 70, 1605–1612. https://doi.org/10.1111/all.12758

Cheng, H.-C., Ulane, C.M., Burke, R.E., 2010. Clinical progression in Parkinson disease and the neurobiology of axons. Ann Neurol 67, 715–725. https://doi.org/10.1002/ana.21995

Cheong, J.L.Y., de Pablo-Fernandez, E., Foltynie, T., Noyce, A.J., 2020. The Association Between Type 2 Diabetes Mellitus and Parkinson's Disease. JPD 10, 775–789. https://doi.org/10.3233/JPD-191900

Chou, R., Peterson, K., Helfand, M., 2004. Comparative efficacy and safety of skeletal muscle relaxants for spasticity and musculoskeletal conditions: a systematic review. J.Pain Symptom Manage. 28, 140–175. https://doi.org/10.1016/j.jpainsymman.2004.05.002

Connolly, B.S., Lang, A.E., 2014. Pharmacological treatment of Parkinson disease: a review. JAMA 311, 1670–1683. https://doi.org/10.1001/jama.2014.3654

Cook, L., Schulze, J., Naito, A., Alcalay, R.N., 2021. The Role of Genetic Testing for Parkinson's Disease. Curr Neurol Neurosci Rep 21, 17. https://doi.org/10.1007/s11910-021-01100-7

Courtois, É., Nguyen, T.T.H., Fournier, A., Carcaillon-Bentata, L., Moutengou, É., Escolano, S., Tubert-Bitter, P., Elbaz, A., Thiébaut, A.C.M., Ahmed, I., 2022. Identifying Protective Drugs for Parkinson's Disease in Health-Care Databases Using Machine Learning. Mov Disord. https://doi.org/10.1002/mds.29205

Crosby, N.J., Deane, K., Clarke, C.E., 2003. Amantadine for dyskinesia in Parkinson's disease. Cochrane Database of Systematic Reviews 2010. https://doi.org/10.1002/14651858.CD003467

Davies, N.M., Holmes, M.V., Davey Smith, G., 2018. Reading Mendelian randomisation studies: a guide, glossary, and checklist for clinicians. BMJ 362, k601. https://doi.org/10.1136/bmj.k601

de Bie, R.M.A., Clarke, C.E., Espay, A.J., Fox, S.H., Lang, A.E., 2020. Initiation of pharmacological therapy in Parkinson's disease: when, why, and how. Lancet Neurol 19, 452–461. https://doi.org/10.1016/S1474-4422(20)30036-3

de Germay, S., Conte, C., Rascol, O., Montastruc, J.-L., Lapeyre-Mestre, M., 2020. β-Adrenoceptor Drugs and Parkinson's Disease: A Nationwide Nested Case-Control Study. CNS Drugs 34, 763–772. https://doi.org/10.1007/s40263-020-00736-2

de Lau, L.M.L., Koudstaal, P.J., Hofman, A., Breteler, M.M.B., 2006. Subjective complaints precede Parkinson disease: the rotterdam study. Arch Neurol 63, 362–365. https://doi.org/10.1001/archneur.63.3.noc50312

De Stefano, L., D'Onofrio, B., Gandolfo, S., Bozzalla Cassione, E., Mauro, D., Manzo, A., Ciccia, F., Bugatti, S., 2023. Seronegative rheumatoid

arthritis: one year in review 2023. Clin Exp Rheumatol 41, 554–564. https://doi.org/10.55563/clinexprheumatol/go7g26
Desai, R.J., Solomon, D.H., Shadick, N., Iannaccone, C., Kim, S.C., 2016. Identification of smoking using Medicare data--a validation study of claims-based algorithms. Pharmacoepidemiol Drug Saf 25, 472–475. https://doi.org/10.1002/pds.3953
Dorsey, E.R., Sherer, T., Okun, M.S., Bloem, B.R., 2018. The Emerging Evidence of the Parkinson Pandemic. J Parkinsons Dis 8, S3–S8. https://doi.org/10.3233/JPD-181474
Elfving, P., Kononoff, A., Huhtakangas, J., Kautiainen, H., Savolainen, E., Arstila, L., Barantseva, J., Rannio, T., Niinisalo, H., Puolitaival, A., Soininen, K., Kariniemi, S., Oksaranta, M., Kaipiainen-Seppänen, O., 2023. Incidence of seropositive rheumatoid arthritis in population-based studies in Northern Savo, Finland, during 1980-2020. Rheumatol Int 43, 659–666. https://doi.org/10.1007/s00296-022-05268-0
EMA Press release, 2007. European Medicines Agency recommends suspension of marketing authorisations for carisoprodol-containing medicinal products [WWW Document]. URL https://www.ema.europa.eu/en/news/european-medicines-agency-recommends-suspension-marketing-authorisations-carisoprodol-containing (accessed 6.8.23).
Espay, A.J., Morgante, F., Merola, A., Fasano, A., Marsili, L., Fox, S.H., Bezard, E., Picconi, B., Calabresi, P., Lang, A.E., 2018. Levodopa-induced dyskinesia in Parkinson disease: Current and evolving concepts. Ann Neurol 84, 797–811. https://doi.org/10.1002/ana.25364
Fahn, S., 2008. The history of dopamine and levodopa in the treatment of Parkinson's disease. Mov Disord 23 Suppl 3, S497-508. https://doi.org/10.1002/mds.22028
Favalli, E.G., Biggioggero, M., Crotti, C., Becciolini, A., Raimondo, M.G., Meroni, P.L., 2019. Sex and Management of Rheumatoid Arthritis. Clin Rev Allergy Immunol 56, 333–345. https://doi.org/10.1007/s12016-018-8672-5
FimeaWeb [WWW Document], 2023. URL https://www.fimea.fi/web/en/databases_and_registers/fimeaweb (accessed 6.1.23).
Fiory, F., Perruolo, G., Cimmino, I., Cabaro, S., Pignalosa, F.C., Miele, C., Beguinot, F., Formisano, P., Oriente, F., 2019. The Relevance of

Insulin Action in the Dopaminergic System. Front Neurosci 13, 868. https://doi.org/10.3389/fnins.2019.00868
Ford, B., 2010. Pain in Parkinson's disease. Mov Disord 25 Suppl 1, S98-103. https://doi.org/10.1002/mds.22716
Fox, S.H., Lang, A.E., 2008. Levodopa-related motor complications--phenomenology. Mov Disord 23 Suppl 3, S509-514. https://doi.org/10.1002/mds.22021
Furu, K., Wettermark, B., Andersen, M., Martikainen, J.E., Almarsdottir, A.B., Sørensen, H.T., 2010. The Nordic countries as a cohort for pharmacoepidemiological research. Basic Clin.Pharmacol.Toxicol. 106, 86–94. https://doi.org/10.1111/j.1742-7843.2009.00494.x
Fuso, L., Mores, N., Valente, S., Malerba, M., Montuschi, P., 2013. Long-acting beta-agonists and their association with inhaled corticosteroids in COPD. Curr Med Chem 20, 1477–1495. https://doi.org/10.2174/0929867311320120003
Gallo, V., Vineis, P., Cancellieri, M., Chiodini, P., Barker, R.A., Brayne, C., Pearce, N., Vermeulen, R., Panico, S., Bueno-de-Mesquita, B., Vanacore, N., Forsgren, L., Ramat, S., Ardanaz, E., Arriola, L., Peterson, J., Hansson, O., Gavrila, D., Sacerdote, C., Sieri, S., Kühn, T., Katzke, V.A., van der Schouw, Y.T., Kyrozis, A., Masala, G., Mattiello, A., Perneczky, R., Middleton, L., Saracci, R., Riboli, E., 2019. Exploring causality of the association between smoking and Parkinson's disease. Int.J.Epidemiol. 48, 912–925. https://doi.org/10.1093/ije/dyy230
Gardner, R.C., Burke, J.F., Nettiksimmons, J., Goldman, S., Tanner, C.M., Yaffe, K., 2015. Traumatic brain injury in later life increases risk for Parkinson disease. Ann Neurol 77, 987–995. https://doi.org/10.1002/ana.24396
GBD 2016 Parkinson's Disease Collaborators, 2018. Global, regional, and national burden of Parkinson's disease, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol 17, 939–953. https://doi.org/10.1016/S1474-4422(18)30295-3
GBD 2019 Tobacco Collaborators, 2021. Spatial, temporal, and demographic patterns in prevalence of smoking tobacco use and attributable disease burden in 204 countries and territories, 1990-2019: a systematic analysis from the Global Burden of Disease Study 2019. Lancet 397, 2337–2360. https://doi.org/10.1016/S0140-6736(21)01169-7

Gelb, D.J., Oliver, E., Gilman, S., 1999. Diagnostic criteria for Parkinson disease. Arch Neurol 56, 33–39. https://doi.org/10.1001/archneur.56.1.33
Ghanavatian, S., Derian, A., 2023a. Tizanidine., in: StatPearls. StatPearls Publishing, Treasure Island (FL).
Ghanavatian, S., Derian, A., 2023b. Baclofen., in: StatPearls. StatPearls Publishing, Treasure Island (FL).
Gibb, W.R., Lees, A.J., 1988. The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease. J.Neurol.Neurosurg.Psychiatry. 51, 745–752.
GINA, 2022. Global Strategy for Asthma Management and Prevention.
Giorgianni, F., Ernst, P., Dell'Aniello, S., Suissa, S., Renoux, C., 2020. β2-Agonists and the Incidence of Parkinson Disease. Am J Epidemiol 189, 801–810. https://doi.org/10.1093/aje/kwaa012
Gissler, M., Haukka, J., 2004. Finnish health and social welfare registers in epidemiological research. Norsk Epidemiologi 14, 113–120.
Goedert, M., Spillantini, M.G., Del Tredici, K., Braak, H., 2013. 100 years of Lewy pathology. Nat Rev Neurol 9, 13–24. https://doi.org/10.1038/nrneurol.2012.242
GOLD, 2023. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (2023 report).
Gonzalez-Latapi, P., Marras, C., 2022. Epidemiological Evidence for an Immune Component of Parkinson's Disease. J Parkinsons Dis 12, S29–S43. https://doi.org/10.3233/JPD-223180
Gronich, N., Abernethy, D.R., Auriel, E., Lavi, I., Rennert, G., Saliba, W., 2018. β2-adrenoceptor agonists and antagonists and risk of Parkinson's disease. Mov Disord 33, 1465–1471. https://doi.org/10.1002/mds.108
Guo, X., Chong, L., Zhang, X., Li, R., 2022. Immunosuppressants contribute to a reduced risk of Parkinson's disease in rheumatoid arthritis. Int J Epidemiol 51, 1328–1338. https://doi.org/10.1093/ije/dyac085
Ha, A.D., Jankovic, J., 2012. Pain in Parkinson's disease. Mov Disord 27, 485–491. https://doi.org/10.1002/mds.23959
Haahtela, T., 2006. A 10 year asthma programme in Finland: major change for the better. Thorax 61, 663–670. https://doi.org/10.1136/thx.2005.055699
Harding, Z., Wilkinson, T., Stevenson, A., Horrocks, S., Ly, A., Schnier, C., Breen, D.P., Rannikmäe, K., Sudlow, C.L.M., 2019. Identifying Parkinson's disease and parkinsonism cases using routinely

collected healthcare data: A systematic review. PLoS ONE 14, e0198736. https://doi.org/10.1371/journal.pone.0198736
Healy, D.G., Falchi, M., O'Sullivan, S.S., Bonifati, V., Durr, A., Bressman, S., Brice, A., Aasly, J., Zabetian, C.P., Goldwurm, S., Ferreira, J.J., Tolosa, E., Kay, D.M., Klein, C., Williams, D.R., Marras, C., Lang, A.E., Wszolek, Z.K., Berciano, J., Schapira, A.H.V., Lynch, T., Bhatia, K.P., Gasser, T., Lees, A.J., Wood, N.W., 2008. Phenotype, genotype, and worldwide genetic penetrance of LRRK2-associated Parkinson's disease: a case-control study. Lancet Neurol 7, 583–590. https://doi.org/10.1016/S1474-4422(08)70117-0
Hedya, S.A., Safar, M.M., Bahgat, A.K., 2019. Hydroxychloroquine antiparkinsonian potential: Nurr1 modulation versus autophagy inhibition. Behav.Brain Res. 365, 82–88.
Hernán, M.A., Takkouche, B., Caamaño-Isorna, F., Gestal-Otero, J.J., 2002. A meta-analysis of coffee drinking, cigarette smoking, and the risk of Parkinson's disease. Ann Neurol 52, 276–284. https://doi.org/10.1002/ana.10277
Hernandez, D.G., Reed, X., Singleton, A.B., 2016. Genetics in Parkinson disease: Mendelian versus non-Mendelian inheritance. J Neurochem 139 Suppl 1, 59–74. https://doi.org/10.1111/jnc.13593
Hirsch, L., Jette, N., Frolkis, A., Steeves, T., Pringsheim, T., 2016. The Incidence of Parkinson's Disease: A Systematic Review and Meta-Analysis. Neuroepidemiology 46, 292–300. https://doi.org/10.1159/000445751
Hopfner, F., Höglinger, G.U., Kuhlenbäumer, G., Pottegård, A., Wod, M., Christensen, K., Tanner, C.M., Deuschl, G., 2020. β-adrenoreceptors and the risk of Parkinson's disease. Lancet Neurol. 19, 247–254.
Hopfner, F., Wod, M., Höglinger, G.U., Blaabjerg, M., Rösler, T.W., Kuhlenbäumer, G., Christensen, K., Deuschl, G., Pottegård, A., 2019. Use of β2-adrenoreceptor agonist and antagonist drugs and risk of Parkinson disease. Neurology 93, e135–e142. https://doi.org/10.1212/WNL.0000000000007694
Horsager, J., Andersen, K.B., Knudsen, K., Skjærbæk, C., Fedorova, T.D., Okkels, N., Schaeffer, E., Bonkat, S.K., Geday, J., Otto, M., Sommerauer, M., Danielsen, E.H., Bech, E., Kraft, J., Munk, O.L., Hansen, S.D., Pavese, N., Göder, R., Brooks, D.J., Berg, D., Borghammer, P., 2020. Brain-first versus body-first Parkinson's disease: a multimodal imaging case-control study. Brain 143, 3077–3088. https://doi.org/10.1093/brain/awaa238

Hough, K.P., Curtiss, M.L., Blain, T.J., Liu, R.-M., Trevor, J., Deshane, J.S., Thannickal, V.J., 2020. Airway Remodeling in Asthma. Front Med (Lausanne) 7, 191. https://doi.org/10.3389/fmed.2020.00191

Hughes, A.J., Daniel, S.E., Lees, A.J., 2001. Improved accuracy of clinical diagnosis of Lewy body Parkinson's disease. Neurology 57, 1497–1499. https://doi.org/10.1212/WNL.57.8.1497

Hughes, R.C., Polgar, J.G., Weightman, D., Walton, J.N., 1971. Levodopa in Parkinsonism: the effects of withdrawal of anticholinergic drugs. Br.Med.J. 2, 487–491.

Jaakkola, J.J.K., Hernberg, S., Lajunen, T.K., Sripaijboonkij, P., Malmberg, L.P., Jaakkola, M.S., 2019. Smoking and lung function among adults with newly onset asthma. BMJ Open Respir Res 6, e000377. https://doi.org/10.1136/bmjresp-2018-000377

Jafari, S., Etminan, M., Aminzadeh, F., Samii, A., 2013. Head injury and risk of Parkinson disease: a systematic review and meta-analysis. Mov Disord 28, 1222–1229. https://doi.org/10.1002/mds.25458

Jankovic, J., 2013. Medical treatment of dystonia. Mov Disord 28, 1001–1012. https://doi.org/10.1002/mds.25552

Jankovic, J., 2008. Parkinson's disease: clinical features and diagnosis. Journal of Neurology, Neurosurgery & Psychiatry 79, 368–376. https://doi.org/10.1136/jnnp.2007.131045

Jankovic, J., 2005. Motor fluctuations and dyskinesias in Parkinson's disease: Clinical manifestations. Mov Disord. 20, S11–S16. https://doi.org/10.1002/mds.20458

Jankovic, J., Tan, E.K., 2020. Parkinson's disease: etiopathogenesis and treatment. J Neurol Neurosurg Psychiatry 91, 795–808. https://doi.org/10.1136/jnnp-2019-322338

Jia, F., Fellner, A., Kumar, K.R., 2022. Monogenic Parkinson's Disease: Genotype, Phenotype, Pathophysiology, and Genetic Testing. Genes 13, 471. https://doi.org/10.3390/genes13030471

Johnson, M., 2006. Molecular mechanisms of β2-adrenergic receptor function, response, and regulation. Journal of Allergy and Clinical Immunology 117, 18–24. https://doi.org/10.1016/j.jaci.2005.11.012

Joutsa, J., Gardberg, M., Röyttä, M., Kaasinen, V., 2014. Diagnostic accuracy of parkinsonism syndromes by general neurologists. Parkinsonism Relat Disord 20, 840–844. https://doi.org/10.1016/j.parkreldis.2014.04.019

Kaasinen, V., 2017. Parkinsonin taudin varhainen toteaminen ja uudet diagnostiset kriteerit. Lääketieteellinen Aikakauskirja Duodecim 133, 1265–71.
Kaasinen, V., Nurmi, E., Bergman, J., Eskola, O., Solin, O., Sonninen, P., Rinne, J.O., 2001. Personality traits and brain dopaminergic function in Parkinson's disease. Proc Natl Acad Sci U S A 98, 13272–13277. https://doi.org/10.1073/pnas.231313198
Kainu, A., Rouhos, A., Sovijärvi, A., Lindqvist, A., Sarna, S., Lundbäck, B., 2013. COPD in Helsinki, Finland: socioeconomic status based on occupation has an important impact on prevalence. Scand J Public Health 41, 570–578. https://doi.org/10.1177/1403494813484554
Kandinov, B., Giladi, N., Korczyn, A.D., 2009. Smoking and tea consumption delay onset of Parkinson's disease. Parkinsonism Relat Disord 15, 41–46. https://doi.org/10.1016/j.parkreldis.2008.02.011
Kang, J., Eun, Y., Jang, W., Cho, M.H., Han, K., Jung, J., Kim, Y., Kim, G.-T., Shin, D.W., Kim, H., 2023. Rheumatoid Arthritis and Risk of Parkinson Disease in Korea. JAMA Neurol. https://doi.org/10.1001/jamaneurol.2023.0932
Kartik, S., Pal, R., Chaudhary, M.J., Nath, R., Kumar, M., Binwal, M., Bawankule, D.U., 2023. Neuroprotective role of chloroquine via modulation of autophagy and neuroinflammation in MPTP-induced Parkinson's disease. Inflammopharmacology 31, 927–941. https://doi.org/10.1007/s10787-023-01141-z
Kasten, M., Hartmann, C., Hampf, J., Schaake, S., Westenberger, A., Vollstedt, E.-J., Balck, A., Domingo, A., Vulinovic, F., Dulovic, M., Zorn, I., Madoev, H., Zehnle, H., Lembeck, C.M., Schawe, L., Reginold, J., Huang, J., König, I.R., Bertram, L., Marras, C., Lohmann, K., Lill, C.M., Klein, C., 2018. Genotype-Phenotype Relations for the Parkinson's Disease Genes Parkin, PINK1, DJ1: MDSGene Systematic Review. Mov Disord 33, 730–741. https://doi.org/10.1002/mds.27352
Katzenschlager, R., Sampaio, C., Costa, J., Lees, A., 2003. Anticholinergics for symptomatic management of Parkinson's disease. Cochrane Database Syst Rev 2002, CD003735. https://doi.org/10.1002/14651858.CD003735
Kent, B.D., Mitchell, P.D., McNicholas, W.T., 2011. Hypoxemia in patients with COPD: cause, effects, and disease progression. Int J Chron Obstruct Pulmon Dis 6, 199–208. https://doi.org/10.2147/COPD.S10611
Keränen, T., Marttila, R., 2002. Parkinsonin taudin lääkehoito. Kapseli 30.

Keshtkarjahromi, M., Abraham, D.S., Gruber-Baldini, A.L., Schrader, K., Reich, S.G., Savitt, J.M., Von Coelln, R., Shulman, L.M., 2022. Confirming Parkinson Disease Diagnosis: Patterns of Diagnostic Changes by Movement Disorder Specialists. Parkinsons Dis 2022, 5535826. https://doi.org/10.1155/2022/5535826

Kieburtz, K., 2008. Therapeutic strategies to prevent motor complications in Parkinson's disease. J Neurol 255 Suppl 4, 42–45. https://doi.org/10.1007/s00415-008-4007-4

Kim, C.H., Han, B.S., Moon, J., Kim, D.J., Shin, J., Rajan, S., Nguyen, Q.T., Sohn, M., Kim, W.G., Han, M., Jeong, I., Kim, K.S., Lee, E.H., Tu, Y., Naffin-Olivos, J.L., Park, C.H., Ringe, D., Yoon, H.S., Petsko, G.A., Kim, K.S., 2015. Nuclear receptor Nurr1 agonists enhance its dual functions and improve behavioral deficits in an animal model of Parkinson's disease. Proc.Natl.Acad.Sci.U.S.A. 112, 8756–8761. https://doi.org/10.1073/pnas.1509742112

Klein, C., Westenberger, A., 2012. Genetics of Parkinson's disease. Cold Spring Harb Perspect Med 2, a008888. https://doi.org/10.1101/cshperspect.a008888

Kogure, T., Tatsumi, T., Kaneko, Y., Okamoto, K., 2008. Rheumatoid arthritis accompanied by Parkinson disease. J Clin Rheumatol 14, 192–193. https://doi.org/10.1097/RHU.0B013E318178825f

Koponen, M., Paakinaho, A., Lin, J., Hartikainen, S., Tolppanen, A.-M., 2022. Identification of Drugs Associated with Lower Risk of Parkinson's Disease Using a Systematic Screening Approach in a Nationwide Nested Case-Control Study. Clin Epidemiol 14, 1217–1227. https://doi.org/10.2147/CLEP.S381289

Laugesen, K., Ludvigsson, J.F., Schmidt, M., Gissler, M., Valdimarsdottir, U.A., Lunde, A., Sørensen, H.T., 2021. Nordic Health Registry-Based Research: A Review of Health Care Systems and Key Registries. Clin Epidemiol 13, 533–554. https://doi.org/10.2147/CLEP.S314959

Lees, A.J., Shaw, K.M., Stern, G.M., 1978. Baclofen in Parkinson's disease. J.Neurol.Neurosurg.Psychiatry. 41, 707–708.

Lestón Pinilla, L., Ugun-Klusek, A., Rutella, S., De Girolamo, L.A., 2021. Hypoxia Signaling in Parkinson's Disease: There Is Use in Asking "What HIF?". Biology (Basel) 10. https://doi.org/10.3390/biology10080723

Li, C., Ou, R., Shang, H., 2021. Rheumatoid arthritis decreases risk for Parkinson's disease: a Mendelian randomization study. NPJ Parkinsons Dis. 7, 17–x. https://doi.org/10.1038/s41531-021-00166-x

Li, C.-H., Chen, W.-C., Liao, W.-C., Tu, C.-Y., Lin, C.-L., Sung, F.-C., Chen, C.-H., Hsu, W.-H., 2015. The association between chronic obstructive pulmonary disease and Parkinson's disease: a nationwide population-based retrospective cohort study. QJM 108, 39–45. https://doi.org/10.1093/qjmed/hcu136

Li, X., Li, W., Liu, G., Shen, X., Tang, Y., 2015. Association between cigarette smoking and Parkinson's disease: A meta-analysis. Arch Gerontol Geriatr 61, 510–516. https://doi.org/10.1016/j.archger.2015.08.004

Li, X., Sundquist, J., Sundquist, K., 2012. Subsequent risks of Parkinson disease in patients with autoimmune and related disorders: a nationwide epidemiological study from Sweden. Neurodegener Dis. 10, 277–284. https://doi.org/10.1159/000333222

Liu, B., Svenningsson, P., Ludvigsson, J.F., Lundholm, C., Wallin, J., Larsson, H., Sjölander, A., Williams, D.M., Pedersen, N.L., Wirdefeldt, K., 2023. β2-Adrenoreceptor Agonists, Montelukast, and Parkinson Disease Risk. Ann Neurol 93, 1023–1028. https://doi.org/10.1002/ana.26638

Lund, J.L., Richardson, D.B., Stürmer, T., 2015. The active comparator, new user study design in pharmacoepidemiology: historical foundations and contemporary application. Curr Epidemiol Rep 2, 221–228. https://doi.org/10.1007/s40471-015-0053-5

Lv, Y.-Q., Yuan, L., Sun, Y., Dou, H.-W., Su, J.-H., Hou, Z.-P., Li, J.-Y., Li, W., 2022. Long-term hyperglycemia aggravates α-synuclein aggregation and dopaminergic neuronal loss in a Parkinson's disease mouse model. Transl Neurodegener 11, 14. https://doi.org/10.1186/s40035-022-00288-z

Macleod, A.D., Henery, R., Nwajiugo, P.C., Scott, N.W., Caslake, R., Counsell, C.E., 2018. Age-related selection bias in Parkinson's disease research: are we recruiting the right participants? Parkinsonism Relat Disord 55, 128–133. https://doi.org/10.1016/j.parkreldis.2018.05.027

Maetzler, W., Hausdorff, J.M., 2012. Motor signs in the prodromal phase of Parkinson's disease. Mov Disord 27, 627–633. https://doi.org/10.1002/mds.24973

Magistrelli, L., Comi, C., 2020. Beta2-Adrenoceptor Agonists in Parkinson's Disease and Other Synucleinopathies. J Neuroimmune Pharmacol 15, 74–81. https://doi.org/10.1007/s11481-018-09831-0

Magrinelli, F., Picelli, A., Tocco, P., Federico, A., Roncari, L., Smania, N., Zanette, G., Tamburin, S., 2016. Pathophysiology of Motor Dysfunction in Parkinson's Disease as the Rationale for Drug

Treatment and Rehabilitation. Parkinsons Dis. 2016, 9832839. https://doi.org/10.1155/2016/9832839
Mahlknecht, P., Marini, K., Werkmann, M., Poewe, W., Seppi, K., 2022. Prodromal Parkinson's disease: hype or hope for disease-modification trials? Transl Neurodegener 11, 11. https://doi.org/10.1186/s40035-022-00286-1
Marras, C., Pequeno, P., Austin, P.C., Gershon, A.S., Iqbal, J., Rochon, P.A., Lang, A.E., 2020. Beta Agonists and Progression of Parkinson's Disease in Older Adults: A Retrospective Cohort Study. Mov Disord 35, 1275–1277. https://doi.org/10.1002/mds.28085
McGuinness, B.W., 1983. A double-blind comparison in general practice of a combination tablet containing orphenadrine citrate and paracetamol ('Norgesic') with paracetamol alone. J.Int.Med.Res. 11, 42–45. https://doi.org/10.1177/030006058301100109
Mckee, A.C., Daneshvar, D.H., 2015. The neuropathology of traumatic brain injury. Handb Clin Neurol 127, 45–66. https://doi.org/10.1016/B978-0-444-52892-6.00004-0
Meara, J., Bhowmick, B.K., Hobson, P., 1999. Accuracy of diagnosis in patients with presumed Parkinson's disease. Age Ageing 28, 99–102. https://doi.org/10.1093/ageing/28.2.99
Meds75+ [WWW Document], 2023. URL https://www.fimea.fi/web/en/databases_and_registeries/medicines_information/database_of_medication_for_older_persons (accessed 6.14.23).
Minakaki, G., Krainc, D., Burbulla, L.F., 2020. The Convergence of Alpha-Synuclein, Mitochondrial, and Lysosomal Pathways in Vulnerability of Midbrain Dopaminergic Neurons in Parkinson's Disease. Front. Cell Dev. Biol. 8, 580634. https://doi.org/10.3389/fcell.2020.580634
Mittal, S., Bjørnevik, K., Im, D.S., Flierl, A., Dong, X., Locascio, J.J., Abo, K.M., Long, E., Jin, M., Xu, B., Xiang, Y.K., Rochet, J.C., Engeland, A., Rizzu, P., Heutink, P., Bartels, T., Selkoe, D.J., Caldarone, B.J., Glicksman, M.A., Khurana, V., Schüle, B., Park, D.S., Riise, T., Scherzer, C.R., 2017. β2-Adrenoreceptor is a regulator of the α-synuclein gene driving risk of Parkinson's disease. Science 357, 891–898. https://doi.org/10.1126/science.aaf3934
Miyake, Y., Tanaka, K., Fukushima, W., Sasaki, S., Kiyohara, C., Tsuboi, Y., Yamada, T., Oeda, T., Miki, T., Kawamura, N., Sakae, N., Fukuyama, H., Hirota, Y., Nagai, M., 2010. Case-control study of risk of Parkinson's disease in relation to hypertension,

hypercholesterolemia, and diabetes in Japan. J Neurol Sci 293, 82–86. https://doi.org/10.1016/j.jns.2010.03.002
Möttönen, T., Hannonen, P., Leirisalo-Repo, M., Nissilä, M., Kautiainen, H., Korpela, M., Laasonen, L., Julkunen, H., Luukkainen, R., Vuori, K., Paimela, L., Blåfield, H., Hakala, M., Ilva, K., Yli-Kerttula, U., Puolakka, K., Järvinen, P., Hakola, M., Piirainen, H., Ahonen, J., Pälvimäki, I., Forsberg, S., Koota, K., Friman, C., 1999. Comparison of combination therapy with single-drug therapy in early rheumatoid arthritis: a randomised trial. FIN-RACo trial group. Lancet 353, 1568–1573.
Nadeem, H., Zhou, B., Goldman, D., Romley, J., 2022. Association between use of ß2-adrenergic receptor agonists and incidence of Parkinson's disease: Retrospective cohort analysis. PLoS One 17, e0276368. https://doi.org/10.1371/journal.pone.0276368
Nielsen, M., Bårnes, C.B., Ulrik, C.S., 2015. Clinical characteristics of the asthma-COPD overlap syndrome--a systematic review. Int J Chron Obstruct Pulmon Dis 10, 1443–1454. https://doi.org/10.2147/COPD.S85363
Nielsen, M.W., Søndergaard, B., Kjøller, M., Hansen, E.H., 2008. Agreement between self-reported data on medicine use and prescription records vary according to method of analysis and therapeutic group. J Clin Epidemiol 61, 919–924. https://doi.org/10.1016/j.jclinepi.2007.10.021
Noyce, A.J., Bestwick, J.P., Silveira-Moriyama, L., Hawkes, C.H., Giovannoni, G., Lees, A.J., Schrag, A., 2012. Meta-analysis of early nonmotor features and risk factors for Parkinson disease. Ann Neurol 72, 893–901. https://doi.org/10.1002/ana.23687
Nyström, H., Nordström, A., Nordström, P., 2016. Risk of Injurious Fall and Hip Fracture up to 26 y before the Diagnosis of Parkinson Disease: Nested Case-Control Studies in a Nationwide Cohort. PLoS Med 13, e1001954. https://doi.org/10.1371/journal.pmed.1001954
Paalanen, K., Puolakka, K., Nikiphorou, E., Hannonen, P., Sokka, T., 2021. Is seronegative rheumatoid arthritis true rheumatoid arthritis? A nationwide cohort study. Rheumatology (Oxford) 60, 2391–2395. https://doi.org/10.1093/rheumatology/keaa623
Paalanen, K., Rannio, K., Rannio, T., Asikainen, J., Hannonen, P., Sokka, T., 2019. Does early seronegative arthritis develop into rheumatoid arthritis? A 10-year observational study. Clin Exp Rheumatol 37, 37–43.

Pang, S.Y.-Y., Ho, P.W.-L., Liu, H.-F., Leung, C.-T., Li, L., Chang, E.E.S., Ramsden, D.B., Ho, S.-L., 2019. The interplay of aging, genetics and environmental factors in the pathogenesis of Parkinson's disease. Transl Neurodegener 8, 23. https://doi.org/10.1186/s40035-019-0165-9

Papi, A., Brightling, C., Pedersen, S.E., Reddel, H.K., 2018. Asthma. Lancet 391, 783–800. https://doi.org/10.1016/S0140-6736(17)33311-1

Parkinson's disease: Current Care Guidelines, 2022. Working group set up by the Finnish Medical Society Duodecim and the Finnish Neurological Society. Helsinki: The Finnish Medical Society Duodecim, 2022.

PD MED Collaborative Group, Gray, R., Ives, N., Rick, C., Patel, S., Gray, A., Jenkinson, C., McIntosh, E., Wheatley, K., Williams, A., Clarke, C.E., 2014. Long-term effectiveness of dopamine agonists and monoamine oxidase B inhibitors compared with levodopa as initial treatment for Parkinson's disease (PD MED): a large, open-label, pragmatic randomised trial. Lancet 384, 1196–1205. https://doi.org/10.1016/S0140-6736(14)60683-8

Peter, I., Dubinsky, M., Bressman, S., Park, A., Lu, C., Chen, N., Wang, A., 2018. Anti-Tumor Necrosis Factor Therapy and Incidence of Parkinson Disease Among Patients With Inflammatory Bowel Disease. JAMA Neurol 75, 939–946. https://doi.org/10.1001/jamaneurol.2018.0605

Peterson, L., Ismond, K.P., Chapman, E., Flood, P., 2014. Potential benefits of therapeutic use of β2-adrenergic receptor agonists in neuroprotection and Parkinsonμs disease. J Immunol Res 2014, 103780. https://doi.org/10.1155/2014/103780

Picelli, A., Santamato, A., Chemello, E., Cinone, N., Cisari, C., Gandolfi, M., Ranieri, M., Smania, N., Baricich, A., 2019. Adjuvant treatments associated with botulinum toxin injection for managing spasticity: An overview of the literature. Ann Phys Rehabil Med 62, 291–296. https://doi.org/10.1016/j.rehab.2018.08.004

Pitcher, T.L., Macaskill, M.R., Anderson, T.J., 2014. Trends in antiparkinsonian medication use in new zealand: 1995-2011. Parkinsons Dis. 2014, 379431. https://doi.org/10.1155/2014/379431

Poewe, W., 1998. Adjuncts to levodopa therapy: dopamine agonists. Neurology 50, S23-6; discussion S44-48. https://doi.org/10.1212/wnl.50.6_suppl_6.s23

Poewe, W., Seppi, K., Tanner, C.M., Halliday, G.M., Brundin, P., Volkmann, J., Schrag, A.E., Lang, A.E., 2017. Parkinson disease. Nat.Rev.Dis.Primers 3, 17013. https://doi.org/10.1038/nrdp.2017.13

Politis, M., 2014. Neuroimaging in Parkinson disease: from research setting to clinical practice. Nat Rev Neurol 10, 708–722. https://doi.org/10.1038/nrneurol.2014.205

Poly, T.N., Islam, M.M., Walther, B.A., Yang, H.-C., Nguyen, P.-A., Huang, C.-W., Shabbir, S.-A., Li, Y.-C.J., 2017. Exploring the Association between Statin Use and the Risk of Parkinson's Disease: A Meta-Analysis of Observational Studies. Neuroepidemiology 49, 142–151. https://doi.org/10.1159/000480401

Potashkin, J., Huang, X., Becker, C., Chen, H., Foltynie, T., Marras, C., 2020. Understanding the links between cardiovascular disease and Parkinson's disease. Mov.Disord. 35, 55–74. https://doi.org/10.1002/mds.27836

Pringsheim, T., Jette, N., Frolkis, A., Steeves, T.D.L., 2014. The prevalence of Parkinson's disease: A systematic review and meta-analysis. Movement Disorders 29, 1583–1590. https://doi.org/10.1002/mds.25945

Psaty, B.M., Koepsell, T.D., Lin, D., Weiss, N.S., Siscovick, D.S., Rosendaal, F.R., Pahor, M., Furberg, C.D., 1999. Assessment and control for confounding by indication in observational studies. J Am Geriatr Soc 47, 749–754. https://doi.org/10.1111/j.1532-5415.1999.tb01603.x

Quik, M., Perez, X.A., Bordia, T., 2012. Nicotine as a potential neuroprotective agent for Parkinson's disease. Mov Disord 27, 947–957. https://doi.org/10.1002/mds.25028

Racette, B.A., Gross, A., Vouri, S.M., Camacho-Soto, A., Willis, A.W., Searles Nielsen, S., 2018. Immunosuppressants and risk of Parkinson disease. Ann.Clin.Transl.Neurol. 5, 870–875. https://doi.org/10.1002/acn3.580

Rascol, O., Fabbri, M., Poewe, W., 2021. Amantadine in the treatment of Parkinson's disease and other movement disorders. Lancet Neurol 20, 1048–1056. https://doi.org/10.1016/S1474-4422(21)00249-0

Ray, W.A., 2003. Evaluating medication effects outside of clinical trials: new-user designs. Am J Epidemiol 158, 915–920. https://doi.org/10.1093/aje/kwg231

Rempenault, C., Combe, B., Barnetche, T., Gaujoux-Viala, C., Lukas, C., Morel, J., Hua, C., 2018. Metabolic and cardiovascular benefits of hydroxychloroquine in patients with rheumatoid arthritis: a

systematic review and meta-analysis. Ann.Rheum.Dis. 77, 98–103. https://doi.org/10.1136/annrheumdis-2017-211836
Ritz, B., Lee, P.-C., Lassen, C.F., Arah, O.A., 2014. Parkinson disease and smoking revisited: ease of quitting is an early sign of the disease. Neurology 83, 1396–1402. https://doi.org/10.1212/WNL.0000000000000879
Rizzo, G., Copetti, M., Arcuti, S., Martino, D., Fontana, A., Logroscino, G., 2016. Accuracy of clinical diagnosis of Parkinson disease: A systematic review and meta-analysis. Neurology 86, 566–576. https://doi.org/10.1212/WNL.0000000000002350
Rong, B., Liu, Y., Li, M., Fu, T., Gao, W., Liu, H., 2018. Correlation of serum levels of HIF-1α and IL-19 with the disease progression of COPD: a retrospective study. Int J Chron Obstruct Pulmon Dis 13, 3791–3803. https://doi.org/10.2147/COPD.S177034
Rugbjerg, K., Friis, S., Ritz, B., Schernhammer, E.S., Korbo, L., Olsen, J.H., 2009. Autoimmune disease and risk for Parkinson disease: a population-based case-control study. Neurology 73, 1462–1468. https://doi.org/10.1212/WNL.0b013e3181c06635
Rugbjerg, K., Ritz, B., Korbo, L., Martinussen, N., Olsen, J.H., 2008. Risk of Parkinson's disease after hospital contact for head injury: population based case-control study. BMJ 337, a2494. https://doi.org/10.1136/bmj.a2494
Ruokolainen, O., Heloma, A., Jousilahti, P., Lahti, J., Pentala-Nikulainen, O., Rahkonen, O., Puska, P., 2019. Thirty-eight-year trends of educational differences in smoking in Finland. Int J Public Health 64, 853–860. https://doi.org/10.1007/s00038-019-01228-x
Sääksjärvi, K., Knekt, P., Männistö, S., Lyytinen, J., Jääskeläinen, T., Kanerva, N., Heliövaara, M., 2014. Reduced risk of Parkinson's disease associated with lower body mass index and heavy leisure-time physical activity. Eur J Epidemiol 29, 285–292. https://doi.org/10.1007/s10654-014-9887-2
Salas, M., Hofman, A., Stricker, B.H., 1999. Confounding by indication: an example of variation in the use of epidemiologic terminology. Am.J.Epidemiol. 149, 981–983. https://doi.org/10.1093/oxfordjournals.aje.a009758
Sarkar, M., Niranjan, N., Banyal, P.K., 2017. Mechanisms of hypoxemia. Lung India 34, 47–60. https://doi.org/10.4103/0970-2113.197116

Savica, R., Grossardt, B.R., Ahlskog, J.E., Rocca, W.A., 2012. Metabolic markers or conditions preceding Parkinson's disease: a case-control study. Mov Disord 27, 974–979. https://doi.org/10.1002/mds.25016

Schapira, A.H.V., Chaudhuri, K.R., Jenner, P., 2017. Non-motor features of Parkinson disease. Nat Rev Neurosci 18, 435–450. https://doi.org/10.1038/nrn.2017.62

Schapira, A.H.V., Emre, M., Jenner, P., Poewe, W., 2009. Levodopa in the treatment of Parkinson's disease. Eur J Neurol 16, 982–989. https://doi.org/10.1111/j.1468-1331.2009.02697.x

Schneeweiss, S., 2006. Sensitivity analysis and external adjustment for unmeasured confounders in epidemiologic database studies of therapeutics. Pharmacoepidemiol Drug Saf 15, 291–303. https://doi.org/10.1002/pds.1200

Schrag, A., Ben-Shlomo, Y., Quinn, N., 2002. How valid is the clinical diagnosis of Parkinson's disease in the community? J.Neurol.Neurosurg.Psychiatry. 73, 529–534. https://doi.org/10.1136/jnnp.73.5.529

Schrag, A., Bohlken, J., Dammertz, L., Teipel, S., Hermann, W., Akmatov, M.K., Bätzing, J., Holstiege, J., 2022. Widening the Spectrum of Risk Factors, Comorbidities, and Prodromal Features of Parkinson Disease. JAMA Neurol. https://doi.org/10.1001/jamaneurol.2022.3902

Schrag, A., Horsfall, L., Walters, K., Noyce, A., Petersen, I., 2015. Prediagnostic presentations of Parkinson's disease in primary care: a case-control study. Lancet Neurol. 14, 57–64. https://doi.org/10.1016/S1474-4422(14)70287-X

Schrag, A., Quinn, N., 2000. Dyskinesias and motor fluctuations in Parkinson's disease. A community-based study. Brain 123 (Pt 11), 2297–2305. https://doi.org/10.1093/brain/123.11.2297

Schrezenmeier, E., Dörner, T., 2020. Mechanisms of action of hydroxychloroquine and chloroquine: implications for rheumatology. Nat.Rev.Rheumatol. 16, 155–166. https://doi.org/10.1038/s41584-020-0372-x

Searles Nielsen, S., Gallagher, L.G., Lundin, J.I., Longstreth, W.T.J., Smith-Weller, T., Franklin, G.M., Swanson, P.D., Checkoway, H., 2012. Environmental tobacco smoke and Parkinson's disease. Mov Disord 27, 293–296. https://doi.org/10.1002/mds.24012

Searles Nielsen, S., Gross, A., Camacho-Soto, A., Willis, A.W., Racette, B.A., 2018. β2-adrenoreceptor medications and risk of Parkinson disease. Ann Neurol 84, 683–693. https://doi.org/10.1002/ana.25341

Shu, L., Zhang, Y., Sun, Q., Pan, H., Tang, B., 2019. A Comprehensive Analysis of Population Differences in LRRK2 Variant Distribution in Parkinson's Disease. Front Aging Neurosci 11, 13. https://doi.org/10.3389/fnagi.2019.00013

Sidransky, E., Nalls, M.A., Aasly, J.O., Aharon-Peretz, J., Annesi, G., Barbosa, E.R., Bar-Shira, A., Berg, D., Bras, J., Brice, A., Chen, C.-M., Clark, L.N., Condroyer, C., De Marco, E.V., Dürr, A., Eblan, M.J., Fahn, S., Farrer, M.J., Fung, H.-C., Gan-Or, Z., Gasser, T., Gershoni-Baruch, R., Giladi, N., Griffith, A., Gurevich, T., Januario, C., Kropp, P., Lang, A.E., Lee-Chen, G.-J., Lesage, S., Marder, K., Mata, I.F., Mirelman, A., Mitsui, J., Mizuta, I., Nicoletti, G., Oliveira, C., Ottman, R., Orr-Urtreger, A., Pereira, L.V., Quattrone, A., Rogaeva, E., Rolfs, A., Rosenbaum, H., Rozenberg, R., Samii, A., Samaddar, T., Schulte, C., Sharma, M., Singleton, A., Spitz, M., Tan, E.-K., Tayebi, N., Toda, T., Troiano, A.R., Tsuji, S., Wittstock, M., Wolfsberg, T.G., Wu, Y.-R., Zabetian, C.P., Zhao, Y., Ziegler, S.G., 2009. Multicenter analysis of glucocerebrosidase mutations in Parkinson's disease. N Engl J Med 361, 1651–1661. https://doi.org/10.1056/NEJMoa0901281

Silva, G.E., Sherrill, D.L., Guerra, S., Barbee, R.A., 2004. Asthma as a risk factor for COPD in a longitudinal study. Chest 126, 59–65. https://doi.org/10.1378/chest.126.1.59

Simonet, C., Bestwick, J., Jitlal, M., Waters, S., Ben-Joseph, A., Marshall, C.R., Dobson, R., Marrium, S., Robson, J., Jacobs, B.M., Belete, D., Lees, A.J., Giovannoni, G., Cuzick, J., Schrag, A., Noyce, A.J., 2022. Assessment of Risk Factors and Early Presentations of Parkinson Disease in Primary Care in a Diverse UK Population. JAMA Neurol 79, 359–369. https://doi.org/10.1001/jamaneurol.2022.0003

Simonis, G., Fuhrmann, J.T., Strasser, R.H., 2007. Meta-analysis of heart valve abnormalities in Parkinson's disease patients treated with dopamine agonists. Mov Disord 22, 1936–1942. https://doi.org/10.1002/mds.21639

Singh, A., Hussain, S., Akkala, S., Klugarová, J., Pokorná, A., Klugar, M., Walters, E.H., Hopper, I., Campbell, J.A., Taylor, B., Antony, B., 2022. Beta-adrenergic drugs and risk of Parkinson's disease: A systematic review and meta-analysis. Ageing Res Rev 80, 101670. https://doi.org/10.1016/j.arr.2022.101670

Sipilä, J.O.T., Kaasinen, V., 2022. Parkinsonin taudin epidemiologia ja genetiikka Suomessa. Lääketieteellinen Aikakauskirja Duodecim 138, 1377–84.
Smedby, B., Schiøler, G., 2006. Health Classifications in the Nordic Countries : historic development in a national and international perspective 2006 = Hälsoklassifikationer i de nordiska länderna : den historiska utvecklingen i ett nationellt och internationellt perspektiv 2006. Nordisk Medicinalstatistisk Komité, København.
Smolen, J.S., Aletaha, D., Barton, A., Burmester, G.R., Emery, P., Firestein, G.S., Kavanaugh, A., McInnes, I.B., Solomon, D.H., Strand, V., Yamamoto, K., 2018. Rheumatoid arthritis. Nat.Rev.Dis.Primers 4, 18001. https://doi.org/10.1038/nrdp.2018.1
Smolen, J.S., Landewé, R.B.M., Bijlsma, J.W.J., Burmester, G.R., Dougados, M., Kerschbaumer, A., McInnes, I.B., Sepriano, A., van Vollenhoven, R.F., de Wit, M., Aletaha, D., Aringer, M., Askling, J., Balsa, A., Boers, M., den Broeder, A.A., Buch, M.H., Buttgereit, F., Caporali, R., Cardiel, M.H., De Cock, D., Codreanu, C., Cutolo, M., Edwards, C.J., van Eijk-Hustings, Y., Emery, P., Finckh, A., Gossec, L., Gottenberg, J.E., Hetland, M.L., Huizinga, T.W.J., Koloumas, M., Li, Z., Mariette, X., Müller-Ladner, U., Mysler, E.F., da Silva, J.A.P., Poór, G., Pope, J.E., Rubbert-Roth, A., Ruyssen-Witrand, A., Saag, K.G., Strangfeld, A., Takeuchi, T., Voshaar, M., Westhovens, R., van der Heijde, D., 2020. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. Ann.Rheum.Dis. 79, 685–699. https://doi.org/10.1136/annrheumdis-2019-216655
Song, Y., Racette, B.A., Camacho-Soto, A., Searles Nielsen, S., 2023. Biologic targets of prescription medications and risk of neurodegenerative disease in United States Medicare beneficiaries. PLoS One 18, e0285011. https://doi.org/10.1371/journal.pone.0285011
Stamey, W., Davidson, A., Jankovic, J., 2008. Shoulder pain: a presenting symptom of Parkinson disease. J Clin Rheumatol 14, 253–254. https://doi.org/10.1097/RHU.0b013e3181826d43
Stürmer, T., Wang, T., Golightly, Y.M., Keil, A., Lund, J.L., Jonsson Funk, M., 2020. Methodological considerations when analysing and interpreting real-world data. Rheumatology (Oxford) 59, 14–25. https://doi.org/10.1093/rheumatology/kez320
Sugiyama, D., Nishimura, K., Tamaki, K., Tsuji, G., Nakazawa, T., Morinobu, A., Kumagai, S., 2010. Impact of smoking as a risk factor for

developing rheumatoid arthritis: a meta-analysis of observational studies. Ann Rheum Dis 69, 70–81. https://doi.org/10.1136/ard.2008.096487
Sund, R., 2012. Quality of the Finnish Hospital Discharge Register: a systematic review. Scand.J.Public Health 40, 505–515. https://doi.org/10.1177/1403494812456637
Sung, Y.F., Liu, F.C., Lin, C.C., Lee, J.T., Yang, F.C., Chou, Y.C., Lin, C.L., Kao, C.H., Lo, H.Y., Yang, T.Y., 2016. Reduced Risk of Parkinson Disease in Patients With Rheumatoid Arthritis: A Nationwide Population-Based Study. Mayo Clin.Proc. 91, 1346–1353.
Swierkot, J., Szechiński, J., 2006. Methotrexate in rheumatoid arthritis. Pharmacol Rep 58, 473–492.
Tai, Y.-C., Lin, C.-H., 2020. An overview of pain in Parkinson's disease. Clin Park Relat Disord 2, 1–8. https://doi.org/10.1016/j.prdoa.2019.11.004
Tamim, H., Monfared, A.A., LeLorier, J., 2007. Application of lag-time into exposure definitions to control for protopathic bias. Pharmacoepidemiol.Drug Saf. 16, 250–258. https://doi.org/10.1002/pds.1360
Tan, E.-K., Chao, Y.-X., West, A., Chan, L.-L., Poewe, W., Jankovic, J., 2020. Parkinson disease and the immune system — associations, mechanisms and therapeutics. Nat.Rev.Neurol. 16, 303–318. https://doi.org/10.1038/s41582-020-0344-4
Tanner, C.M., Kamel, F., Ross, G.W., Hoppin, J.A., Goldman, S.M., Korell, M., Marras, C., Bhudhikanok, G.S., Kasten, M., Chade, A.R., Comyns, K., Richards, M.B., Meng, C., Priestley, B., Fernandez, H.H., Cambi, F., Umbach, D.M., Blair, A., Sandler, D.P., Langston, J.W., 2011. Rotenone, paraquat, and Parkinson's disease. Environ Health Perspect 119, 866–872. https://doi.org/10.1289/ehp.1002839
Tolosa, E., Garrido, A., Scholz, S.W., Poewe, W., 2021. Challenges in the diagnosis of Parkinson's disease. The Lancet Neurology 20, 385–397. https://doi.org/10.1016/S1474-4422(21)00030-2
Tolosa, E., Martí, M.J., Valldeoriola, F., Molinuevo, J.L., 1998. History of levodopa and dopamine agonists in Parkinson's disease treatment. Neurology 50, S2-10; discussion S44-48. https://doi.org/10.1212/wnl.50.6_suppl_6.s2
Tolosa, E., Wenning, G., Poewe, W., 2006. The diagnosis of Parkinson's disease. Lancet Neurol 5, 75–86. https://doi.org/10.1016/S1474-4422(05)70285-4

Tuominen, J.A., Bjørnevik, K., Romanowska, J., Solheim, M.H., Grydeland, T.B., Cortese, M., Scherzer, C.R., Riise, T., Igland, J., 2023. Beta2-adrenoreceptor agonists and long-term risk of Parkinson's disease. Parkinsonism Relat Disord 110, 105389. https://doi.org/10.1016/j.parkreldis.2023.105389

Vaidya, B., Dhamija, K., Guru, P., Sharma, S.S., 2021. Parkinson's disease in women: Mechanisms underlying sex differences. Eur J Pharmacol 895, 173862. https://doi.org/10.1016/j.ejphar.2021.173862

Van Den Eeden, S.K., Tanner, C.M., Bernstein, A.L., Fross, R.D., Leimpeter, A., Bloch, D.A., Nelson, L.M., 2003. Incidence of Parkinson's disease: variation by age, gender, and race/ethnicity. Am.J.Epidemiol. 157, 1015–1022.

Wagstaff, A.J., Bryson, H.M., 1997. Tizanidine. A review of its pharmacology, clinical efficacy and tolerability in the management of spasticity associated with cerebral and spinal disorders. Drugs 53, 435–452. https://doi.org/10.2165/00003495-199753030-00007

Waldman, H.J., 1994. Centrally acting skeletal muscle relaxants and associated drugs. J Pain Symptom Manage 9, 434–441. https://doi.org/10.1016/0885-3924(94)90199-6

Wermuth, L., Cui, X., Greene, N., Schernhammer, E., Ritz, B., 2015. Medical Record Review to Differentiate between Idiopathic Parkinson's Disease and Parkinsonism: A Danish Record Linkage Study with 10 Years of Follow-Up. Parkinsons Dis. 2015, 781479. https://doi.org/10.1155/2015/781479

WHO Collaborating Centre for Drug Statistics Methodology, 2023. Guidelines for ATC classification and DDD assignment 2023.

WHOCC - ATC/DDD Index [WWW Document], 2023. URL https://www.whocc.no/atc_ddd_index/ (accessed 6.2.23).

WHOCC - Definition and general considerations [WWW Document], 2022. URL https://www.whocc.no/ddd/definition_and_general_considera/ (accessed 5.13.22).

WHOCC - List of DDDs combined products [WWW Document], 2023. URL https://www.whocc.no/ddd/list_of_ddds_combined_products/ (accessed 8.1.23).

Wickremaratchi, M.M., Ben-Shlomo, Y., Morris, H.R., 2009. The effect of onset age on the clinical features of Parkinson's disease. Eur J Neurol 16, 450–456. https://doi.org/10.1111/j.1468-1331.2008.02514.x

Wirdefeldt, K., Adami, H.-O., Cole, P., Trichopoulos, D., Mandel, J., 2011. Epidemiology and etiology of Parkinson's disease: a review of the evidence. Eur J Epidemiol 26 Suppl 1, S1-58. https://doi.org/10.1007/s10654-011-9581-6

Witenko, C., Moorman-Li, R., Motycka, C., Duane, K., Hincapie-Castillo, J., Leonard, P., Valaer, C., 2014. Considerations for the appropriate use of skeletal muscle relaxants for the management of acute low back pain. P T 39, 427–435.

Witoelar, A., Jansen, I.E., Wang, Y., Desikan, R.S., Gibbs, J.R., Blauwendraat, C., Thompson, W.K., Hernandez, D.G., Djurovic, S., Schork, A.J., Bettella, F., Ellinghaus, D., Franke, A., Lie, B.A., McEvoy, L.K., Karlsen, T.H., Lesage, S., Morris, H.R., Brice, A., Wood, N.W., Heutink, P., Hardy, J., Singleton, A.B., Dale, A.M., Gasser, T., Andreassen, O.A., Sharma, M., International Parkinson's Disease Genomics Consortium (IPDGC), N.A.B.E.C. (NABEC), and United Kingdom Brain Expression Consortium (UKBEC) Investigators, 2017. Genome-wide Pleiotropy Between Parkinson Disease and Autoimmune Diseases. JAMA Neurol. 74, 780–792. https://doi.org/10.1001/jamaneurol.2017.0469

Wouters, E.F.M., Reynaert, N.L., Dentener, M.A., Vernooy, J.H.J., 2009. Systemic and local inflammation in asthma and chronic obstructive pulmonary disease: is there a connection? Proc Am Thorac Soc 6, 638–647. https://doi.org/10.1513/pats.200907-073DP

Yayan, J., Rasche, K., 2016. Asthma and COPD: Similarities and Differences in the Pathophysiology, Diagnosis and Therapy. Adv Exp Med Biol 910, 31–38. https://doi.org/10.1007/5584_2015_206

Yeh, J.-J., Wei, Y.-F., Lin, C.-L., Hsu, W.-H., 2018. Effect of the asthma-chronic obstructive pulmonary disease syndrome on the stroke, Parkinson's disease, and dementia: a national cohort study. Oncotarget 9, 12418–12431. https://doi.org/10.18632/oncotarget.23811

Yoshida, K., Solomon, D.H., Kim, S.C., 2015. Active-comparator design and new-user design in observational studies. Nat Rev Rheumatol 11, 437–441. https://doi.org/10.1038/nrrheum.2015.30

ORIGINAL PUBLICATIONS (I – III)

I

Incidence of muscle relaxant use in relation to diagnosis of Parkinson's disease.

Paakinaho, A., Karttunen, N., Koponen, M., Taipale, H., Tolppanen, A.-M., Hartikainen, S. and Tiihonen, M.

International Journal of Clinical Pharmacy 42: 336–340, 2020

International Journal of Clinical Pharmacy (2020) 42:336–340
https://doi.org/10.1007/s11096-020-01002-7

SHORT RESEARCH REPORT

Incidence of muscle relaxant use in relation to diagnosis of Parkinson's disease

Anne Paakinaho[1,2] · Niina Karttunen[1,2] · Marjaana Koponen[1,2,3] · Heidi Taipale[1,2] · Anna-Maija Tolppanen[1,2] · Sirpa Hartikainen[1,2] · Miia Tiihonen[1,2]

Received: 9 July 2019 / Accepted: 20 February 2020 / Published online: 6 March 2020

Abstract
Background Parkinson's disease is the second most common neurodegenerative disorder. Motor and non-motor symptoms seem to precede the diagnosis of Parkinson's disease. *Objective* To evaluate the incidence of muscle relaxant use in community-dwelling persons with and without Parkinson's disease from 4 years before to 4 years after the diagnosis of Parkinson's disease. *Method* Nationwide register-based cohort included all community-dwelling Finnish persons who received reimbursement of Parkinson's disease drugs between 2000 and 2015 (N = 17,450) and comparison persons without Parkinson's disease who were matched for age, gender and region of residence (N = 122,694). Data on muscle relaxant use during 1995–2016 were collected from the Prescription Register. *Results* The incidence of muscle relaxant use was higher among persons with Parkinson's disease in comparison to persons without Parkinson's disease from 3 years before the diagnosis until 6 months after the diagnosis. The largest difference in incidence rates was observed at the time of the diagnosis (incidence rate ratio = 2.04, 95% confidence interval = 1.81–2.30). Tizanidine was the most frequently initiated muscle relaxant. *Conclusions* The incidence of muscle relaxant use starts increasing years before the diagnosis of Parkinson's disease but declines after that. It is important to identify the causes of muscle symptoms to avoid unnecessary muscle relaxant use and consequent adverse effects and events.

Keywords Finland · FINPARK cohort · Incidence · Muscle relaxants · Parkinson's disease

Impact on practice statements

- Non-specific muscle symptoms and consequent muscle relaxant use might be preceding symptoms of Parkinson's disease
- Muscle relaxant use could be early sign of Parkinson's disease. To avoid unnecessary use of muscle relaxants reasons causing non-specific muscle symptoms should be investigated thoroughly. Muscle relaxants should be used cautiously especially in older persons with Parkinson's disease due to potential adverse effects and events such as hypotension and falls

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder, with the incidence estimated to be 15 per 100,000 individuals per year [1]. The incidence increases with age, particularly after the age of 60 years [2, 3].

According to a new definition, PD could be divided into preclinical, prodromal, and clinical stages [4]. In the preclinical stage, no signs or symptoms are present yet, despite the neurodegenerative changes that have begun. In the prodromal stage, symptoms and signs are present, but not yet

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s11096-020-01002-7) contains supplementary material, which is available to authorized users.

✉ Miia Tiihonen
miia.tiihonen@uef.fi

[1] Kuopio Research Centre of Geriatric Care, University of Eastern Finland, P.O. Box 1627, 70211 Kuopio, Finland

[2] School of Pharmacy, University of Eastern Finland, Kuopio, Finland

[3] Faculty of Pharmacy and Pharmaceutical Sciences, Centre for Medicine Use and Safety, Monash University, Parkville, VIC, Australia

identified as clinical PD. Motor symptoms such as tremor, shoulder pain or stiffness, and rigidity have been reported to appear 2 years before PD diagnosis [5]. Whether these motor symptoms are treated with symptomatic drugs (e.g. muscle relaxants) has not previously been studied. However, muscle relaxants have potential serious adverse drug effects and events, such as sedation and fatigue, or cardiac arrhythmias [6].

Aims of the study

The aim of this study was to investigate incidence of muscle relaxant use in community-dwelling persons with and without PD from 4 years before to 4 years after the diagnosis of PD.

Ethics approval

According to Finnish legislation, no ethics committee approval was required since persons were not contacted and the data was de-identified. Permission for the data was received from register maintainers.

Method

This nationwide register-based study was based on the FINPARK cohort, which includes all community-dwelling Finnish persons (N = 29,942) who received special reimbursement of PD drugs between 1996 and 2015. Persons were identified from the Special Reimbursement Register which is maintained by the Social Insurance Institution of Finland (SII). This register includes data on chronic diseases diagnosed by a physician. Persons with PD are entitled to a special reimbursement after the SII have accepted the medical certificate from a neurologist. According to the Finnish Current Care Guideline, PD diagnosis must be based on the United Kingdom Parkinson's Disease Society Brain Bank (UKPDSBB) criteria. Persons with diagnoses other than PD (International Statistical Classification of Diseases and Related Health Problems, ICD-10, G20) with the same special reimbursement code (110) (N = 1244), and persons under the age of 35 years were excluded (N = 53) (Supplementary figure). In addition, persons with a diagnosis of diseases that have similar types of symptoms as PD, such as multiple sclerosis, secondary parkinsonism and Alzheimer's disease, within the two-year time window of PD diagnosis were excluded from this study (N = 6962). Diagnoses were obtained from the Special Reimbursement Register and Hospital Discharge Register containing hospital admissions, discharge days with diagnoses as ICD-10 codes [7]. After exclusion of persons, the number of the PD population was 21,683. For every person with PD, 1-7 comparison persons without PD were matched for age, gender and region of residence from the SII database covering all residents (n = 127,505). The matching date, i.e., time of PD diagnosis of the case was assigned as an index date for comparison persons. Persons diagnosed during the years 2000–2015 and their comparison persons were included to allow follow-up time for drug use 5 years before the diagnoses.

The FINPARK cohort combines data from several nationwide registers including the Prescription (1995–2016), the Special Reimbursement (1972–2016) and the Hospital Discharge Register (1972–2016). Comorbid conditions diagnosed before the PD diagnosis or the corresponding date for comparison persons, were derived from the Special Reimbursement Register for each person. Data on cardiovascular diseases included hypertension, coronary artery disease, arrhythmias and heart failure. Diabetes, asthma or chronic obstructive pulmonary disease (COPD) and rheumatoid arthritis and other comparable conditions were also included.

The first purchases of muscle relaxants among persons with and without PD during 1995–2016 were collected from the Prescription Register, which gives information on all reimbursed prescription drug dispensing for community-dwelling persons. The Prescription Register does not include drug use during hospital or public nursing home care. Drugs are categorized according to the Anatomical Therapeutic Chemical (ATC) classification system codes.

The muscle relaxants were defined according to ATC codes M03A, peripherally acting agents including botulinum toxin, and M03B, centrally acting agents including methocarbamol, carisoprodol, chlorzoxazone, orphenadrine, and orphenadrine combined with paracetamol, baclofen, and tizanidine [8]. The muscle relaxants included in this study are only available as prescription drugs in Finland.

As we aimed to investigate incident use of muscle relaxants, a 1-year washout period 4–5 years before the PD diagnosis or corresponding matching date for comparison persons was utilized in order to exclude prevalent users. Persons who were hospitalized over half of the washout period or having stayed over 90 days in the hospital by the end of the washout period were excluded. After exclusions, 17,450 persons with PD and 122,694 persons without PD were included in the final study. The follow-up for the incidence of muscle relaxant use began 4 years before and ended 4 years after the diagnosis of PD or corresponding matching date for comparison persons. The follow-up was censored for the following reasons: initiation of muscle relaxant use, ≥ 90 day hospitalization, death, or end of the study (December 31, 2016), whichever occurred first.

The incidence of muscle relaxant use was defined as having at least one purchase of any muscle relaxant during

the eight-year follow-up period. Incidence rates (IR) were calculated in six-month intervals as initiations per 100 person-years. The IRs were compared with Poisson regression between persons with PD and their comparison persons and the results were reported as incidence rate ratios (IRR) with 95% confidence intervals (CI). The analyses were performed using IBM SPSS statistics 25 and SAS 9.4 software.

Results

The mean age of the study population was 70.9 years (range 34.2–98.2, SD 9.7) at the time of PD diagnosis or corresponding matching date for comparison persons, and over half of the persons (55.9%) were men (Table 1). During the follow-up, 3424 (19.6%) persons with PD initiated muscle relaxant use and 18,639 (15.2%) of comparison persons. In both the PD and the comparison population, female gender and asthma/COPD were more common among users and cardiovascular diseases and diabetes were more frequent among nonusers.

Tizanidine was the most frequently (64.0%) initiated muscle relaxant covering 62.4% of all initiations in persons with PD and 64.3% without PD. Tizanidine was followed by orphenadrine combined with paracetamol (22.2%) and orphenadrine alone (11.7%).

The IRper 100 person-years of muscle relaxant use was higher among persons with PD compared to persons without PD from three years before until six months after the PD diagnosis (Fig. 1a). The difference was largest at the time of the diagnosis (IR in persons with PD 4.50/100 person-years, without PD 2.19/100 person-years) and the IRR = 2.04, 95% CI = 1.81–2.30.

The IR of tizanidine and orphenadrine use was higher in persons with PD from two years before the PD diagnosis and six months after (Fig. 1b, c). At the time of the diagnosis the IR in persons with PD was 3.02/100 person-years for tizanidine and 1.66/100 person-years for orphenadrine, and in persons without PD these were 1.45 and 0.84, respectively. The IRRs were 1.96 (95% CI = 1.62–2.36) for tizanidine and 2.07 (95% CI = 1.79–2.39) for orphenadrine.

Discussion

As far as we know, this is the first study reporting the incidence of muscle relaxant use among community-dwelling persons with PD. The incidence of muscle relaxant use was higher in persons with PD compared to persons without PD from 3 years before to 6 months after the diagnosis of PD. The same characteristics were associated with muscle relaxant use in people with and without PD.

PD diagnosis is challenging at the early stage [9]. Previous studies have reported that motor symptoms appear already 2 years before the diagnosis [5]. Persons with disturbing motor symptoms visit health care providers, including doctors, and may get muscle relaxant prescriptions when these symptoms are not yet possible to identify as PD.

The incidence of muscle relaxant use was at its highest at the time of the diagnosis in persons with PD and the difference in IRs was two-fold in comparison to persons without PD. Consequently, these drugs might have been prescribed as a first aid to relieve symptoms during the diagnostic process. Six months after the diagnosis, the incidence decreased possibly related to the relief of the motor symptoms due to the initiation of anti-Parkinson drugs.

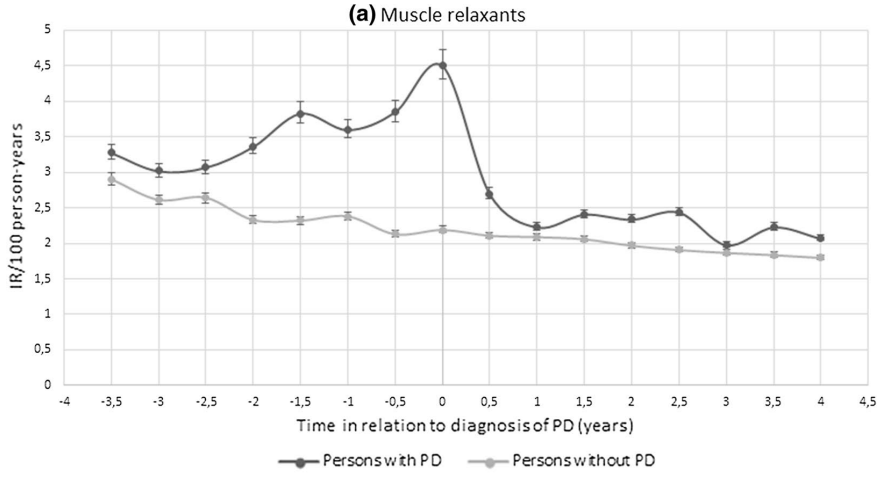
Tizanidine was the most frequently initiated muscle relaxant in the cohort followed by orphenadrine preparations. Common use of tizanidine in our study might reflect the overall prescribing pattern of muscle relaxants in Finland. In addition, decline in the use of anticholinergics, including orphenadrine, in the treatment of PD has been previously

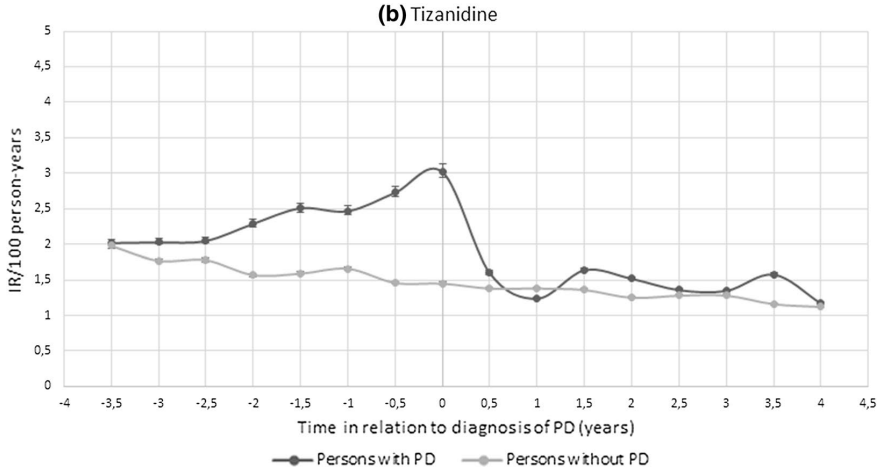
Table 1 Characteristics and comorbidities of the study population and comparison between incident users of muscle relaxants among persons with Parkinson's disease (PD) and comparison persons

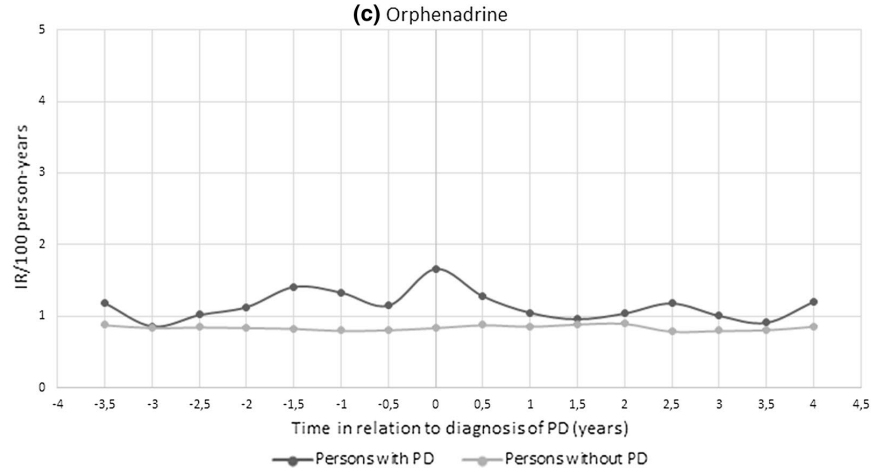
	Persons with PD N = 17,450			Comparison persons N = 122,694		
	Users (n = 3424)	Nonusers (n = 14,026)	*p*	Users (n = 18,639)	Nonusers (n = 104,055)	*P*
Demographic characteristics						
Age, mean (SD)	67.27 (9.89)	71.83 (9.42)	<0.001	67.46 (10.21)	71.51 (9.49)	<0.001
Gender: male, n (%)	1700 (49.6)	8068 (57.5)	<0.001	9533 (51.1)	59,058 (56.8)	<0.001
Comorbidities						
Cardiovascular diseases, n (%)	1202 (35.1)	5818 (41.5)	<0.001	6903 (37.0)	41,377 (39.8)	<0.001
Diabetes, n (%)	318 (9.3)	1511 (10.8)	0.011	1767 (9.5)	10,987 (10.6)	<0.001
Asthma/COPD, n (%)	297 (8.7)	1012 (7.2)	0.004	1700 (9.1)	7795 (7.5)	<0.001
Rheumatoid arthritis, n (%)	117 (3.4)	477 (3.4)	0.963	758 (4.1)	3818 (3.7)	0.008

Comparison is made at the time of PD diagnosis

COPD chronic obstructive pulmonary disease


(a) Muscle relaxants
IR/100 person-years
Time in relation to diagnosis of PD (years)
Persons with PD
Persons without PD


(b) Tizanidine
IR/100 person-years
Time in relation to diagnosis of PD (years)
Persons with PD
Persons without PD


(c) Orphenadrine
IR/100 person-years
Time in relation to diagnosis of PD (years)
Persons with PD
Persons without PD

◂**Fig. 1** Incidence rates (IR) of **a** muscle relaxant, **b** tizanidine and **c** orphenadrine use in persons with Parkinson's disease (PD) and without the disease from four years before the diagnosis to four years after the diagnosis of PD

reported [10]. Tizanidine is an alpha-2 receptor agonist and its main indication is the management of spasticity, commonly caused by upper motor neuron disorders. Adverse effects include sedation, fatigue and bradycardia, symptoms that could consequently increase the risk of falls [6]. Future studies is needed to find out the role of male gender and asthma among as well associations with muscle relaxant use and falls and injurious falls among persons with and without PD.

The main strength of this study is the nationwide cohort which represents community-dwelling persons with PD in Finland. Muscle relaxants are available only as prescription drugs in Finland and thus recorded in the Prescription Register. Limitations were the lack of drug use indication and dosage, types of muscle symptoms in registers, and muscle relaxant use during hospital care.

Conclusion

The incidence of muscle relaxant use was higher in persons with PD than without PD starting from 3 years before the diagnosis implying that muscle symptoms arise already years before the PD diagnosis. It is important to identify the reasons leading to non-specific muscle symptoms to avoid unnecessary use of muscle relaxants and consequent adverse effects and events.

Acknowledgments None.

Funding This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflicts of Interest None.

References

1. Tysnes OB, Storstein A. Epidemiology of Parkinson's disease. J Neural Transm (Vienna). 2017;124:901–5.
2. Van Den Eeden SK, Tanner CM, Bernstein AL, et al. Incidence of Parkinson's disease: variation by age, gender, and race/ethnicity. Am J Epidemiol. 2003;157:1015–22.
3. Twelves D, Perkins KS, Counsell C. Systematic review of incidence studies of Parkinson's disease. Mov Disord. 2003;18:19–31.
4. Berg D, Postuma RB, Adler CH, et al. MDS research criteria for prodromal Parkinson's disease. Mov Disord. 2015;30:1600–11.
5. Schrag A, Horsfall L, Walters K, Noyce A, Petersen I. Prediagnostic presentations of Parkinson's disease in primary care: a case-control study. Lancet Neurol. 2015;14:57–64.
6. Wagstaff AJ, Bryson HM. Tizanidine. A review of its pharmacology, clinical efficacy and tolerability in the management of spasticity associated with cerebral and spinal disorders. Drugs. 1997;53:435–52.
7. Sund R. Quality of the Finnish hospital discharge register: a systematic review. Scand J Public Health. 2012;40:505–15.
8. WHO collaborating centre for drugs statistics methodology, ATC structure and principles, 2019. https://www.whocc.no/atc/structure_and_principles/. Accessed 28 March 2019.
9. Rizzo G, Copetti M, Arcuti S, Martino D, Fontana A, Logroscino G. Accuracy of clinical diagnosis of Parkinson disease: a systematic review and meta-analysis. Neurology. 2016;86:566–76.
10. Pitcher TL, Macaskill MR, Anderson TJ. Trends in antiparkinsonian medication use in New Zealand: 1995–2011. Parkinsons Dis. 2014;2014:379431.

II

Disease-modifying antirheumatic drugs and risk of Parkinson Disease. Nested case-control study of people with rheumatoid arthritis

Paakinaho, A., Koponen, M., Tiihonen M., Kauppi M., Hartikainen, S. and Tolppanen, A.-M.

Neurology 98: e1273-e1281, 2022

Abstract

Background

Epidemiological studies have suggested a link between rheumatoid arthritis and Parkinson's disease (PD). Disease-modifying anti-rheumatic drugs (DMARDs) might explain this association.

Objective

To evaluate the association between DMARDs and risk of PD in persons with rheumatoid arthritis.

Methods

Nested nationwide case-control study was conducted within the Finnish Parkinson's disease (FINPARK) cohort that includes 22,189 Finnish persons with clinically verified PD diagnosed in 1996-2015. The cases had recorded diagnosis of PD in the Special Reimbursement Register and had no exclusion diagnoses whose symptoms may be confused with PD within two years of PD diagnosis. This study included cases with PD diagnosed during 1999-2015 and rheumatoid arthritis diagnosed >3 years before PD. Rheumatoid arthritis was identified using Finnish Care Register for Health Care and Special Reimbursement Register. Cases were matched with up to seven control persons by age, sex, duration of rheumatoid arthritis and region. DMARDs were categorised into five classes and data on purchased prescriptions was identified from the Prescription Register since 1995. Associations were studied with conditional logistic regression adjusted for confounders.

Results

Altogether 315 cases with PD and 1,571 matched controls were included. Majority (> 60%) were women and median duration of rheumatoid arthritis on matching date was 11.6 years for controls and 12.6 years for cases. Use of DMARDs was not associated with risk of PD with three-year lag period applied between exposure and outcome, except chloroquine/hydroxychloroquine which associated with decreased risk (adjusted odds ratio 0.74; 95% confidence interval 0.56-0.97). Other DMARDs, including sulfasalazine, methotrexate, gold preparations and immunosuppressants, were not associated with PD.

Discussion

Our results suggest that the lower risk of PD in people with rheumatoid arthritis is not explained by DMARD use as these drugs in general did not modify the risk of PD among persons with rheumatoid arthritis. Association between chloroquine/hydroxychloroquine and lower risk of PD as well as the possible underlying mechanisms should be further investigated.

Classification of evidence: This study provides Class II evidence that in individuals with rheumatoid arthritis using DMARDs, only chloroquine/hydroxychloroquine was associated with a potentially decreased risk of developing PD (adjusted OR 0.74, 95% CI 0.56-0.97).

Introduction

Rheumatoid arthritis has been linked to lower risk of Parkinson's disease (PD)[1-3], although some studies have also observed an increased risk of PD in people with rheumatoid arthritis[4], or no association between rheumatoid arthritis and PD[5].

One suggested explanation for the protective association are medications used to treat rheumatoid arthritis[1]. Disease-modifying anti-rheumatic drugs (DMARDs), such as methotrexate and sulfasalazine, inhibit the rheumatic inflammation and progression of structural joint damage[6], and they could modify the risk of PD by interfering with immune system dysfunction, which has been suggested to be present in PD[7]. However, there is very little research on the association of DMARDs with risk of PD. Although one study demonstrated lower risk of PD in users and nonusers of DMARDs with rheumatoid arthritis compared to people without rheumatoid arthritis[1], that study did not compare the risk between DMARD users and nonusers with rheumatoid arthritis. A case-control study which investigated several DMARDs reported that use of either azathioprine, leflunomide or mycophenolate were associated with lower risk of PD[8].

The primary research question of our study is whether use of different DMARDs is associated with risk of PD. We investigated this in a nested nationwide case-control study restricted to persons with rheumatoid arthritis diagnosed at least 3 years before clinically verified PD. This restriction of study population allowed us to minimize confounding by indication of DMARD treatment. To control for increased contact with healthcare professionals due to diagnostic process of PD, which could differentially affect the exposure in cases, we applied a three-year lag period between DMARD use and PD diagnosis. In addition, due to the long onset period of PD, it is unlikely that DMARDs initiated within close proximity to PD diagnosis would impact the risk.

Methods

FINPARK study population

A nested case-control study was conducted within the Finnish Parkinson's disease (FINPARK) cohort that contains all community-dwelling Finnish persons who received special reimbursement for PD drugs in 1996-2015 (N=22,189). These persons were identified using the Special Reimbursement Register which includes information on entitlements to higher reimbursements for drugs because of chronic diseases. PD diagnosis was based on United Kingdom Parkinson's disease Society Brain Bank criteria[9] and exclusion diagnoses for FINPARK cohort has been reported previously[10]. For every person with PD, up to 7 comparison persons without PD were identified from the Social Insurance Institution (SII) database covering all residents and they were matched for age, sex, and region of residence (N=148,009). Each Finnish resident is given a unique personal identification number which enables data linkage across several registers. The FINPARK study has been described in detail previously[10].

Identification of cases and controls for this study

Formation of study population is described in Figure 1. Persons diagnosed with PD in 1999-2015 (N=19,568) were included in this study as drug exposure data were available since 1995 and we used a three-year lag period in exposure assessment. To control for confounding by indication we restricted the study to people who had been diagnosed with rheumatoid arthritis at least three years before PD diagnosis. Rheumatoid arthritis was defined from the Finnish Care Register for Health Care (1987-2012) and Special Reimbursement Register (1972-2012) using International Classification of Diseases (ICD) ICD-9 and ICD-10 codes as described in eTable 1. In addition, ICD-8 codes (1972-1986) were used to get the earliest diagnosis date of rheumatoid arthritis for those who had rheumatoid arthritis based on ICD-9 or ICD-10

codes. Final diagnosis date for rheumatoid arthritis was defined either as the earliest date of the hospitalization, specialized healthcare outpatient visit or as the first date of the entitlement to reimbursement for drugs used to treat rheumatoid arthritis, whichever occurred first.

For each PD case with rheumatoid arthritis (n=318), up to seven controls without PD but with rheumatoid arthritis were matched from the controls of the FINPARK study. Date of the PD diagnosis was defined as the index date. Controls were matched based on sex, age (+/- 2 years) on index date, time since rheumatoid arthritis diagnosis on index date (+/- 2 years) and university hospital district. If no controls were identified from the same district, controls were allowed to come from neighboring district. Same exclusion criteria were applied for cases and controls. In addition, controls were not allowed to have diagnosis of Dementia in Parkinson's disease (ICD-10 code F02.3). The final study population included 315 cases and 1,571 controls. Three cases without matched controls were excluded.

Drug exposure

Data on DMARD and corticosteroid purchases were extracted from the Prescription register since 1995 until the index date. The Prescription register includes data on all reimbursed drug purchases, while drug use during hospital stays or in public nursing homes is not recorded in this register. Drugs are categorized according to Anatomical Therapeutic Chemical (ATC) classification system. Drug use was defined based on ATC codes (eTable 2) and DMARDs were categorized as follows: sulfasalazine (A07EC01), chloroquine (P01BA01) or hydroxychloroquine (P01BA02), gold preparations (M01CB) including auranofin and sodium aurothiomalate and immunosuppressants (L04A) which consist of azathioprine, certolizumab

pegol, ciclosporin, mycophenolic acid and biological DMARDs (bDMARDs): abatacept, adalimumab, anakinra, etanercept, golimumab and leflunomide. Methotrexate (L04AX03) was studied separately from immunosuppressants throughout the study due to its common usage in the treatment of rheumatoid arthritis. Due to small number of bDMARD users during the study period, they were combined with immunosuppressants in the main analysis. In addition, we performed sensitivity analysis investigating bDMARDs as a separate category. Corticosteroids (H02AB) covered prednisolone, prednisone, and methylprednisolone. Dexamethasone was excluded due to low amount of reimbursed purchases. All the above-mentioned drugs are available only as prescription drugs and all reimbursed purchases can be reliably identified from the register. The first date of purchase was determined for each drug or drug group for each person and person was defined as user if there was at least one purchase.

To control for biases caused by 1) prodromal symptoms or ongoing diagnosis process of PD affecting drug exposure, or 2) newly diagnosed rheumatoid arthritis or changes in rheumatoid arthritis pharmacotherapy increasing likelihood of being diagnosed with PD, we applied a three-year lag period for assessing drug exposure. Three years was chosen based on our previous study demonstrating that incidence of muscle relaxants, an indicator of motor symptoms of PD, occurs within this three-year period in FINPARK cohort[11]. In the main analysis drug use was determined prior to three-year lag period indicating that exposure had occurred at least three years before index date. Time before lag period refers to exposure assessment period. Additionally, drug exposure was measured within lag period only (within three years of index date) or without lag period (ever before index date).

Furthermore, exposure histories based on the different types of DMARDs used during the exposure assessment period were derived.

Covariates

Comorbidities that were considered to be associated with exposure and outcome were used as covariates (eTable 3). History of asthma or chronic obstructive pulmonary disease (COPD), stroke, diabetes, cardiovascular diseases including any of the following: hypertension, coronary artery disease, chronic heart failure and chronic arrhythmias, substance abuse and head injury were identified using the Special Reimbursement Register, Care Register for Health Care Register or Prescription Register. Cancer history was derived from Cancer Register using ICD-10 codes from IARC CRG Tools. All covariates were defined until the start of the three-year lag period and ever before index date.

Statistical analyses

Characteristics of cases and controls were compared with χ^2-test for categorical variables. For continuous variables, t-test was applied for normally distributed and Mann-Whitney U test for non-normally distributed data. Conditional logistic regression was used to estimate the unadjusted and adjusted odds ratios (aORs) with 95% confidence intervals (CIs) for the association between exposures and PD. Analyses were conducted with different lag periods i.e., without lag period, with three-year lag and use only during the three-year lag period. We analyzed the association between individual DMARD categories (use vs. no use) to assess the association of specific DMARDs. To account for changes in pharmacotherapy for rheumatoid arthritis (i.e., one person using more than just one type of DMARDs during the exposure assessment period), we grouped the persons based on the types of drugs they had purchased

(sulfasalazine, methotrexate, chloroquine/hydroxychloroquine, gold preparations and immunosuppressants). The association between different exposure histories for DMARDs was investigated in comparison to most common exposure type category. Only categories with >5% frequency were reported.

The minimum detectable ORs for different exposure prevalence levels among controls are shown in eFigure 1. We had 80% power to detect ORs ≥1.41 (or ≤0.71) with exposure prevalence of 50% and ORs ≥1.92 (or ≤0.52) with exposure prevalence of 5% (alpha=0.05).

Analyses were performed with SAS v9.4 (SAS Institute, Cary, North Carolina). Power calculations were performed with Stata MP14.0 using power mcc-function.

Standard Protocol Approvals, Registrations, and Patient Consents

According to Finnish legislation, ethics committee approval or informed consent is not needed, because included persons cannot be identified due to pseudonymised register data, and the persons were not contacted.

Data availability

The data used to conduct this research is not publicly available due to restrictions by the register maintainers and Finnish legislation. However, the data are available from the corresponding author, provided that appropriate permission of the register maintainers is sought and demonstrated.

Results

The characteristics of cases (N=315) and matched controls (N=1,571) are described in Table 1. The age ranged between 46 and 93 years (mean 73.1 years). Most of the study participants were women. Median duration of rheumatoid arthritis on index date was 11.6 years for controls and 12.6 years for cases, respectively. Prevalence of different comorbidities was comparable between PD cases and controls and cardiovascular diseases were the most common comorbidities.

Use of DMARDs and corticosteroids in different time periods are summarized in Table 2. The three most commonly used DMARDs in both cases and controls were sulfasalazine, methotrexate and chloroquine/hydroxychloroquine (Table 2). Gold preparations were used by approximately one quarter of cases and controls during exposure assessment period and immunosuppressant were the least commonly used DMARD. Corticosteroids were used by nearly two thirds of cases and controls during exposure assessment period.

Use of DMARDs or corticosteroids during exposure assessment was not associated with risk of PD except for use of chloroquine/hydroxychloroquine which associated with decreased risk (aOR 0.74; 95% CI 0.56-0.97) (Table 2). The use of bDMARDs was infrequent in the study period, with less than 3% of cases and controls having used before the three-year lag time. They were not associated with risk of PD (aOR 0.98; 95% CI 0.46-2.09).

When any use before the index date was considered, regardless of whether it was initiated during actual exposure assessment or during lag time, the associations were similar. When initiations in the three-year lag period were considered, no associations were observed.

The negative association of chloroquine/hydroxychloroquine was stronger when any use before the index date was considered (aOR 0.69; 95% CI 0.53-0.89) than in the main analysis

with exposure that had occurred before the three-year lag period (aOR 0.74; 95% CI 0.56-0.97).

When changes in DMARDs during exposure assessment period (i.e., exposure histories) were considered, the most common exposure type was sulfasalazine, with 10% prevalence in both cases and controls (Table 3). Second most common was the combination of chloroquine/hydroxychloroquine, methotrexate, and sulfasalazine. The frequency of other types was <10% in cases and controls. No associations were observed between different exposure histories for DMARDs and PD risk when adjusted with different covariates (Table 3).

Classification of Evidence: This study provides Class II evidence that in individuals with rheumatoid arthritis using DMARDs, only chloroquine/hydroxychloroquine was associated with a potentially decreased risk of developing PD (adjusted OR 0.74, 95% CI 0.56-0.97).

Discussion

Studies on the association between DMARDs and risk of PD in population restricted to rheumatoid arthritis are lacking, although they would aid in understanding whether the inverse association between rheumatoid arthritis and PD is explained by DMARD-treatment of rheumatoid arthritis. Our nationwide nested case-control study of people with rheumatoid arthritis found no association between the use of DMARDs or corticosteroids and risk of PD on a general level. However, the use of chloroquine/hydroxychloroquine was associated with lower risk of PD, even when the analyses were restricted to exposure that had occurred at least three years before PD diagnosis.

These results extend the findings of earlier studies which have implied the role of immune system in PD pathogenesis[7]. Genome-wide association studies have shown that autoimmune

diseases, including rheumatoid arthritis, and PD share genetic pathways[12]. Lower risk of PD has been observed in people with rheumatoid arthritis in some[1-3] but not all studies[4,5], and similarly conflicting findings have been reported for systemic lupus erythematosus[4,13], another autoimmune disease. Given these inconsistent findings, it is difficult to conclude whether autoimmune diseases alter the PD pathophysiology and to what extent. However, the evidence of involvement of immune system dysfunction in PD pathogenesis[7] supports the presumption that long-term use of DMARDs, which have anti-inflammatory properties, could explain the reduced risk of PD in rheumatoid arthritis. Surprisingly, the number of pharmacoepidemiological studies on DMARDs is still small.

Differences in our study design prevent direct comparison to earlier studies which have mainly studied how rheumatoid arthritis as a disease is associated with risk of PD[1-5] or how DMARDs are associated with risk of PD without restricting study population to persons with rheumatoid arthritis[8]. We wanted to focus on DMARDs and avoid confounding by indication by restricting study to people with rheumatoid arthritis. This allowed us to evaluate the association of DMARDs and PD instead of rheumatoid arthritis and PD. Secondly, we considered drug exposure that had occurred at least three years before PD diagnosis, since PD has long latency period before actual diagnosis and potentially increased contact with healthcare, as evident from the initiation of muscle relaxants already three years before PD diagnosis[11], can also affect drug exposure. By contrast, previous case-control study[8] applied only one-year lag between drug exposure and PD diagnosis. We also conducted sensitivity analyses considering exposure that had occurred until PD diagnosis and during the lag period. The results of these additional analyses were in line with the main analyses.

In Finland, we have a long-lasting tradition to aim to remission in the treatment of rheumatoid arthritis. Thus, DMARDs have been used actively during the whole study period. Sulfasalazine was the most used DMARD in our study followed by methotrexate and chloroquine/hydroxychloroquine. These three DMARDs, so called Triple therapy, have been the recommended treatment according to Finnish guidelines for rheumatoid arthritis[14]. In addition to individual drugs, we assessed whether exposure histories for different types of DMARDs at least three years before PD diagnosis would differ in the risk of PD but observed no differences compared to sulfasalazine.

Some of the DMARDs have been previously associated with reduced risk of PD. In an earlier case-control study[8], users of azathioprine, leflunomide or mycophenolate, had reduced risk of PD compared to nonusers with or without one-year lag between drug exposure and outcome. However, we did not observe risk reduction for immunosuppressants class in which these drugs, along with bDMARDs, were defined in our study. In a cohort study, people with rheumatoid arthritis had lower risk of PD than those without rheumatoid arthritis regardless of DMARD use[1]. The relative risk reduction was similar in DMARD users and nonusers with rheumatoid arthritis in comparison to persons without rheumatoid arthritis, meaning that use of DMARDs did not explain the protective association of rheumatoid arthritis. Despite differences in study setting, this reflects our results since in general we found no association between DMARDs use and risk of PD among people with rheumatoid arthritis.

In a previous case-control study, corticosteroids were associated with lower risk of PD when the exposure had occurred at least one year before or up to PD diagnosis[8] while we did not observe association between corticosteroids and PD. One explanation for our null result might be that despite their immunosuppressive effects, corticosteroids are aimed to be used

with low dose and only for relatively short-term in the treatment of rheumatoid arthritis due to their possible adverse effects in long-term use, such as osteoporosis[15]. It is possible to reach remission with active use of DMARDs, even without long-term use of systemic corticosteroids.

Our finding on the association between chloroquine/hydroxychloroquine, and lower risk of PD is, however, consistent with the previous case-control study[8], which reported a protective association for hydroxychloroquine when any exposure before PD diagnosis was considered (relative risk=0.77; 95% CI 0.65-0.90), and a weaker association when exposure occurring at least one year before the outcome was investigated (relative risk=0.83; 95% CI 0.68-1.00). This attenuation may imply that the association in that study was partially due to increased healthcare contact in close proximity to PD diagnosis. Our findings provide additional support to this earlier observation as we were able to use longer lag time in exposure assessment.

Neuroprotective potential of chloroquine and hydroxychloroquine has been speculated previously[16,17]. Both chloroquine and hydroxychloroquine, interfere with lysosomal activity and autophagy, can inhibit both innate and adaptive immune processes and reduce production of inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor (TNF)[18]. These immunomodulatory effects could have a role in modulating inflammatory processes in PD. However, methotrexate, the first-line DMARD for rheumatoid arthritis, that is more powerful immunosuppressant than hydroxychloroquine[19], was not associated with risk of PD in our study. Therefore, the protective association of chloroquine/hydroxychloroquine might be explained by other reasons than its immunosuppressive effects. Hydroxychloroquine has been implied to have pleiotropic effects, as it was recently shown to improve lipid profiles and reduce diabetes incidence in rheumatoid arthritis[20], a population in increased risk of cardiovascular diseases[21]. It is possible

that the effects on metabolic and cardiovascular risk factors[22] might partly explain our findings. It should be noted that hydroxychloroquine is better tolerated than chloroquine, and thus it is nowadays more commonly used in the treatment of rheumatoid arthritis[23]. Chloroquine was included in our study because we used drug exposure data since 1995.

The protective association of chloroquine/hydroxychloroquine is also supported by experimental models of PD; chloroquine protected dopaminergic (DA) neurons against 6-hydroxydopamine induced neurotoxicity[17] and hydroxychloroquine ameliorated motor functions of rotenone-induced parkinsonian rats in behavioral tests[16]. Neuroprotective effects of these drugs was suggested to be mediated through orphan nuclear receptor Nurr1, which is important in the development and maintenance of midbrain dopaminergic neurons[24] and whose expression was activated by both chloroquine[17] and hydroxychloroquine[16]. In terms of other neurodegenerative diseases, hydroxychloroquine did not, however, slow the progression of dementia in persons with Alzheimer's disease compared to the placebo in double-blind clinical trial[25].

Our study has several strengths. Definition of PD is based on clinically verified diagnosis. Using large nationwide registries, we could restrict the study population on persons who have the indication to use DMARDs thereby controlling for confounding by indication. Due to long, up to 17 years, exposure assessment time we were able to apply three-year lag period. Short lag period between drug exposure and outcome of PD has been a key limitation in previous studies. If drug exposure is measured too close to the diagnosis of PD, it is more likely to reflect different contact density with prescribers than actual risk factor. Further, as PD progresses slowly over time, immediate exposure just before diagnosis is unlikely to have significant effect on PD pathophysiology.

Our study was based on data on purchased drugs in which case medication adherence is based on presumption. On the other hand, all the drugs included are only available as prescription drugs which minimizes classification bias. DMARDs administered in hospitals, for example infliximab, are not included in the prescription register. However, these drugs are never used as the first, or only, DMARD and every patient getting infliximab is also treated with other DMARD(s). Therefore, the drugs administered in hospital should not have a major impact on our results.

Although we had nationwide data, restriction of analyses to those with rheumatoid arthritis and at least three years of exposure assessment decreased the sample size. This means that we had limited power to detect weak associations. However, the power issue unlikely explains the null findings, as we were able to observe the association between chloroquine/hydroxychloroquine and PD risk and the point estimates for other DMARDs in the main analyses were close to the null. Further, based on the exposure prevalence we do not think that a clinically relevant signal was missed because of lack of power, and restriction of study population aided us to avoid indication bias. We did not perform dose-response or duration of treatment analyses due to limitations posed by the sample size. Some of the newer immunosuppressants included in our study, mainly bDMARDs such as golimumab, have entered the market at the end of the study period, therefore they have been used in lesser extent compared to older DMARDs, such as sulfasalazine, methotrexate, and chloroquine/hydroxychloroquine. Findings of additional analysis regarding bDMARDs should be interpreted cautiously due to limited number of users in our study.

A possible limitation of our study is the lack of information on severity of rheumatoid arthritis which could affect chosen pharmacotherapy and have differential impact on developing PD

regardless of DMARDs use. Our data included both seropositive and seronegative rheumatoid arthritis. This is common approach in register-based studies on rheumatoid arthritis, and unlikely to have major impact on our results.

The sex distribution of our study population may appear surprising considering that PD is more common in men[26]. However, rheumatoid arthritis is more common in women than in men[15], which explains the sex distribution in our study. As the earlier studies on rheumatoid arthritis or other autoimmune rheumatic diseases and the risk of PD[1,4] have reported sex distribution comparable to our study and the findings on the association between rheumatoid arthritis and PD have been inconsistent, it is difficult to speculate whether sex has implications for the analyses. We matched cases and controls by sex and thus our results are unlikely explained by sex.

Linkage of several registers enable to account for multiple confounding factors although adjustment with comorbidities did not change the results. We lacked data on smoking, which has been associated with an increased risk of rheumatoid arthritis[15] and oppositely with decreased risk of PD[27]. However, we used smoking-associated comorbidities, including cancer from Cancer registry, as proxies, but residual confounding is still possible. Additionally, the association between chloroquine/hydroxychloroquine and lower risk of PD can be confounded by another variable that was not identified in our study. The association may also be explained by survival bias: both chloroquine and hydroxychloroquine are old drugs and persons treated with them, especially in monotherapy, might have less severe rheumatoid arthritis and better overall health status than those treated with other DMARDs. However, hydroxychloroquine is also included in the drug-combination with methotrexate and sulfasalazine which is widely used also on moderate and severe rheumatoid arthritis.

In conclusion, the hypothesis that decreased risk of PD among rheumatoid arthritis patients could be explained by use of DMARDs was not confirmed in our study. Further studies on newer DMARDs, especially on bDMARDs such as TNF-α inhibitors and target specific DMARDs (JAK inhibitors), and assessment of dose-response relations between DMARDs and risk of PD are needed. The potential ability of chloroquine/hydroxychloroquine to modify the PD disease process should be studied further.

Appendix 1

Authors

Name	Location	Contribution
Anne Paakinaho, MSc (Pharm)	School of Pharmacy, University of Eastern Finland, Kuopio	Design and conceptualization of the study, analysis and interpretation of the data, drafting and revising the manuscript. Approval of the submitted version.
Marjaana Koponen, PhD (Pharm)	School of Pharmacy, University of Eastern Finland, Kuopio	Design and conceptualization of the study, data preprocessing and analysis supervision, revising the manuscript. Approval of the submitted version.
Miia Tiihonen, PhD (Pharm)	School of Pharmacy, University of Eastern Finland, Kuopio	Design and conceptualization of the study, interpretation of the data, revising the manuscript. Approval of the submitted version.
Markku Kauppi, MD, PhD, Professor of rheumatology	Department of rheumatology, Päijät-Häme Central Hospital, Lahti and Clinicum, Faculty of Medicine, University of Helsinki, Helsinki	Interpretation of the data, revising the manuscript. Approval of the submitted version.

Sirpa Hartikainen, MD, PhD	School of Pharmacy, University of Eastern Finland, Kuopio	Design and conceptualization of the study, interpretation of the data, revising the manuscript. Approval of the submitted version.
Anna-Maija Tolppanen, PhD	School of Pharmacy, University of Eastern Finland, Kuopio	Design and conceptualization of the study, interpretation of the data, revising the manuscript. Approval of the submitted version.

Acknowledgement: This project was funded by the Michael J Fox Foundation for Parkinson's research (grant MJFF-008834 to Anna-Maija Tolppanen, which paid salary for Anne Paakinaho and Marjaana Koponen).

References

1. Sung YF, Liu FC, Lin CC, et al. Reduced Risk of Parkinson Disease in Patients With Rheumatoid Arthritis: A Nationwide Population-Based Study. *Mayo Clin Proc.* 2016;91(10):1346-1353. doi:S0025-6196(16)30365-2 [pii].

2. Rugbjerg K, Friis S, Ritz B, Schernhammer ES, Korbo L, Olsen JH. Autoimmune disease and risk for Parkinson disease: a population-based case-control study. *Neurology.* 2009;73(18):1462-1468. doi:10.1212/WNL.0b013e3181c06635 [doi].

3. Bacelis J, Compagno M, George S, et al. Decreased Risk of Parkinson's Disease After Rheumatoid Arthritis Diagnosis: A Nested Case-Control Study with Matched Cases and Controls. *J Parkinsons Dis.* 2021. doi:10.3233/JPD-202418 [doi].

4. Chang CC, Lin TM, Chang YS, et al. Autoimmune rheumatic diseases and the risk of Parkinson disease: a nationwide population-based cohort study in Taiwan. *Ann Med.* 2018;50(1):83-90. doi:10.1080/07853890.2017.1412088 [doi].

5. Li X, Sundquist J, Sundquist K. Subsequent risks of Parkinson disease in patients with autoimmune and related disorders: a nationwide epidemiological study from Sweden. *Neurodegener Dis.* 2012;10(1-4):277-284. doi:10.1159/000333222 [doi].

6. Smolen JS, Aletaha D, McInnes IB. Rheumatoid arthritis. *Lancet.* 2016;388(10055):2023-2038. doi:S0140-6736(16)30173-8 [pii].

7. Tan E-, Chao Y-, West A, Chan L-, Poewe W, Jankovic J. Parkinson disease and the immune system — associations, mechanisms and therapeutics. *Nat Rev Neurol.* 2020;16(6):303-318.

https://www.scopus.com/inward/record.uri?eid=2-s2.0-85084152766&doi=10.1038%2fs41582-020-0344-4&partnerID=40&md5=67a086a72800f1e26174499cea50e839. Accessed 24 June 2020. doi:10.1038/s41582-020-0344-4.

8. Racette BA, Gross A, Vouri SM, Camacho-Soto A, Willis AW, Searles Nielsen S. Immunosuppressants and risk of Parkinson disease. *Ann Clin Transl Neurol.* 2018;5(7):870-875. doi:10.1002/acn3.580 [doi].

9. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. *J Neurol Neurosurg Psychiatry.* 1992;55(3):181-184. doi:10.1136/jnnp.55.3.181 [doi].

10. Hentilä E, Tiihonen M, Taipale H, Hartikainen S, Tolppanen AM. Incidence of antidepressant use among community dwellers with and without Parkinson's disease - a nationwide cohort study. *BMC Geriatr.* 2021;21(1):202-6. doi:10.1186/s12877-021-02145-6 [doi].

11. Paakinaho A, Karttunen N, Koponen M, et al. Incidence of muscle relaxant use in relation to diagnosis of Parkinson's disease. *Int J Clin Pharm.* 2020. doi:10.1007/s11096-020-01002-7 [doi].

12. Witoelar A, Jansen IE, Wang Y, et al. Genome-wide Pleiotropy Between Parkinson Disease and Autoimmune Diseases. *JAMA Neurol.* 2017;74(7):780-792. doi:10.1001/jamaneurol.2017.0469 [doi].

13. Liu FC, Huang WY, Lin TY, et al. Inverse Association of Parkinson Disease With Systemic Lupus Erythematosus: A Nationwide Population-based Study. *Medicine (Baltimore).* 2015;94(46):e2097. doi:10.1097/MD.0000000000002097 [doi].

14. Möttönen T, Hannonen P, Leirisalo-Repo M, et al. Comparison of combination therapy with single-drug therapy in early rheumatoid arthritis: a randomised trial. FIN-RACo trial group. *Lancet.* 1999;353(9164):1568-1573. doi:S0140673698085134 [pii].

15. Smolen JS, Aletaha D, Barton A, et al. Rheumatoid arthritis. *Nat Rev Dis Primers.* 2018;4:18001. doi:10.1038/nrdp.2018.1 [doi].

16. Hedya SA, Safar MM, Bahgat AK. Hydroxychloroquine antiparkinsonian potential: Nurr1 modulation versus autophagy inhibition. *Behav Brain Res.* 2019;365:82-88. doi:S0166-4328(18)31592-4 [pii].

17. Kim CH, Han BS, Moon J, et al. Nuclear receptor Nurr1 agonists enhance its dual functions and improve behavioral deficits in an animal model of Parkinson's disease. *Proc Natl Acad Sci U S A.* 2015;112(28):8756-8761. doi:10.1073/pnas.1509742112 [doi].

18. Schrezenmeier E, Dörner T. Mechanisms of action of hydroxychloroquine and chloroquine: implications for rheumatology. *Nat Rev Rheumatol.* 2020;16(3):155-166. doi:10.1038/s41584-020-0372-x [doi].

19. Aletaha D, Smolen JS. Diagnosis and Management of Rheumatoid Arthritis: A Review. *JAMA.* 2018;320(13):1360-1372. doi:10.1001/jama.2018.13103 [doi].

20. Rempenault C, Combe B, Barnetche T, et al. Metabolic and cardiovascular benefits of hydroxychloroquine in patients with rheumatoid arthritis: a systematic review and meta-analysis. *Ann Rheum Dis.* 2018;77(1):98-103. doi:10.1136/annrheumdis-2017-211836 [doi].

21. England BR, Thiele GM, Anderson DR, Mikuls TR. Increased cardiovascular risk in rheumatoid arthritis: mechanisms and implications. *BMJ.* 2018;361:k1036. doi:10.1136/bmj.k1036 [doi].

22. Potashkin J, Huang X, Becker C, Chen H, Foltynie T, Marras C. Understanding the links between cardiovascular disease and Parkinson's disease. *Mov Disord.* 2020;35(1):55-74. doi:10.1002/mds.27836 [doi].

23. Shippey EA, Wagler VD, Collamer AN. Hydroxychloroquine: An old drug with new relevance. *Cleve Clin J Med.* 2018;85(6):459-467. doi:10.3949/ccjm.85a.17034 [doi].

24. Jang Y, Kim W, Leblanc P, Kim CH, Kim KS. Potent synthetic and endogenous ligands for the adopted orphan nuclear receptor Nurr1. *Exp Mol Med.* 2021;53(1):19-29. doi:10.1038/s12276-021-00555-5 [doi].

25. Van Gool WA, Weinstein HC, Scheltens P, Walstra GJ. Effect of hydroxychloroquine on progression of dementia in early Alzheimer's disease: an 18-month randomised, double-blind, placebo-controlled study. *Lancet.* 2001;358(9280):455-460. doi:S0140673601056239 [pii].

26. Cerri S, Mus L, Blandini F. Parkinson's Disease in Women and Men: What's the Difference? *J Parkinsons Dis.* 2019;9(3):501-515. doi:10.3233/JPD-191683 [doi].

27. Gallo V, Vineis P, Cancellieri M, et al. Exploring causality of the association between smoking and Parkinson's disease. *Int J Epidemiol.* 2019;48(3):912-925. doi:10.1093/ije/dyy230 [doi].

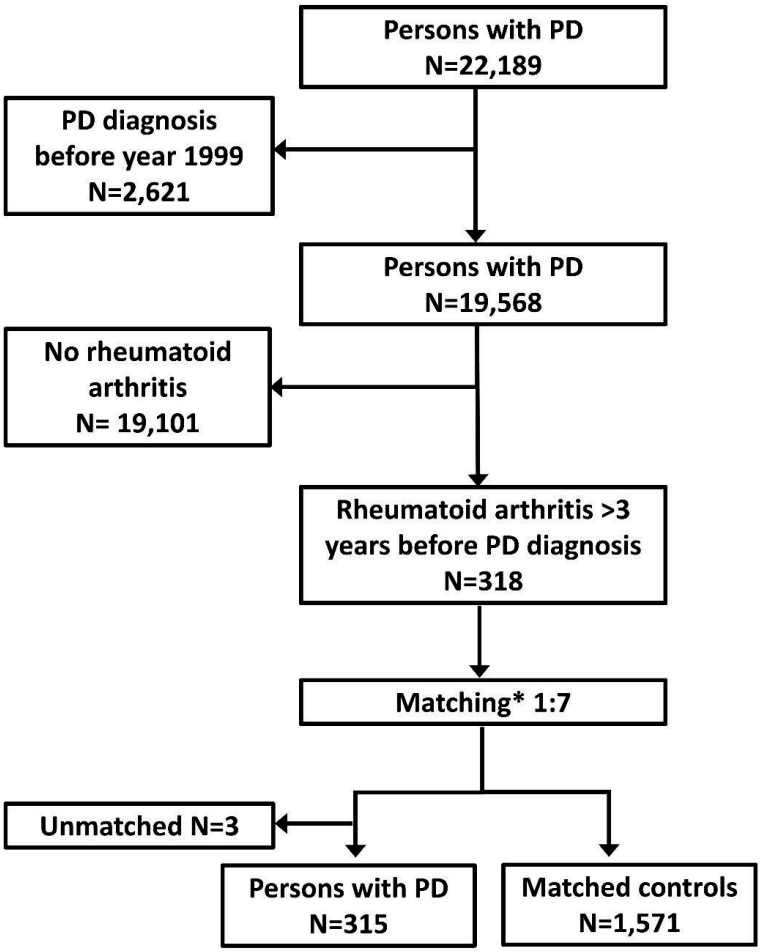


Figure 1. Flow chart of formation of Parkinson's disease (PD) cases and controls.

Table 1. Description of Parkinson's disease (PD) cases and matched controls. Data are given as mean (SD) for age, median (IQR) for duration of rheumatoid arthritis and n (%) for other variables.

	Controls N=1,571	PD cases N=315	P
Age at PD diagnosis (years)	73.1 (7.7)	73.1 (8.2)	1.00[a]
Sex			0.39[b]
Men	539 (34.3)	116 (36.8)	
Women	1032 (65.7)	199 (63.2)	
Duration of rheumatoid arthritis on index date, median years (IQR)	11.6 (7.5–19.2)	12.6 (8.4–20.5)	0.08[c]
University hospital district on index date			0.36[b]
Helsinki	409 (26.0)	74 (23.5)	
Tampere	363 (23.1)	79 (25.1)	
Kuopio	348 (22.2)	61 (19.4)	
Oulu	227 (14.5)	57 (18.1)	
Turku	224 (14.3)	44 (14.0)	
Covariates before three-year lag			
Cardiovascular diseases	639 (40.7)	136 (43.2)	0.41[b]
Asthma or COPD	198 (12.6)	34 (10.8)	0.37[b]
Cancer history	134 (8.5)	24 (7.6)	0.59[b]
Diabetes	132 (8.4)	34 (10.8)	0.17[b]
Head injury	80 (5.1)	13 (4.1)	0.47[b]
Stroke	54 (3.4)	10 (3.2)	0.81[b]
Substance abuse	36 (2.3)	4 (1.3)	0.25[b]

[a] t-test, [b] Chi-Square test, [c] Mann-Whitney U test

COPD=chronic obstructive pulmonary disease, IQR=interquartile range, PD=Parkinson's disease

Table 2. Association between disease-modifying anti-rheumatic drugs (DMARDs) and Parkinson's disease (PD).

	Controls N=1571 n (%)	PD cases N=315 n (%)	P	Unadjusted OR (95% CI)	Adjusted* OR (95% CI)
Drug or drug group	**Use before three-year lag**				
Sulfasalazine	794 (50.5)	161 (51.1)	0.85	1.02 (0.79-1.33)	1.01 (0.78-1.32)
Methotrexate	751 (47.8)	163 (51.8)	0.20	1.17 (0.90-1.52)	1.17 (0.90-1.52)
Chloroquine/ hydroxychloroquine	704 (44.8)	118 (37.5)	0.016	0.73 (0.56-0.96)	0.74 (0.56-0.97)
Gold preparations	388 (24.7)	84 (26.7)	0.46	1.09 (0.82-1.45)	1.11 (0.83-1.47)
Immunosuppressants	231 (14.7)	53 (16.8)	0.34	1.07 (0.76-1.53)	1.06 (0.75-1.51)
Corticosteroids	1062 (67.6)	210 (66.7)	0.75	0.96 (0.73-1.26)	0.98 (0.74-1.29)
	Use only in three-year lag period				
Sulfasalazine	52 (3.3)	9 (2.9)	0.68	0.90 (0.43-1.87)	0.91 (0.44-1.91)
Methotrexate	102 (6.5)	19 (6.0)	0.76	0.98 (0.59-1.63)	0.98 (0.59-1.64)
Chloroquine/ hydroxychloroquine	90 (5.7)	10 (3.2)	0.06	0.57 (0.29-1.12)	0.57 (0.29-1.13)
Gold preparations	27 (1.7)	3 (1.0)	0.32	0.47 (0.14-1.59)	0.46 (0.13-1.56)
Immunosuppressants	68 (4.3)	13 (4.1)	0.87	1.01 (0.55-1.88)	1.03 (0.55-1.91)
Corticosteroids	120 (7.6)	18 (5.7)	0.23	0.76 (0.45-1.28)	0.75 (0.44-1.26)
	Use ever before index date				
Sulfasalazine	846 (53.9)	170 (54.0)	0.97	1.01 (0.78-1.31)	1.01 (0.77-1.31)
Methotrexate	853 (54.3)	182 (57.8)	0.26	1.16 (0.90-1.51)	1.18 (0.91-1.53)
Chloroquine/ hydroxychloroquine	794 (50.5)	128 (40.6)	0.001	0.67 (0.51-0.87)	0.69 (0.53-0.89)
Gold preparations	415 (26.4)	87 (27.6)	0.66	1.03 (0.78-1.37)	1.05 (0.79-1.39)
Immunosuppressants	299 (19.0)	66 (21.0)	0.43	1.06 (0.77-1.46)	1.06 (0.77-1.46)
Corticosteroids	1182 (75.2)	228 (72.4)	0.29	0.87 (0.66-1.16)	0.90 (0.68-1.20)

*Asthma or chronic obstructive pulmonary disease (COPD), cancer history, cardiovascular diseases, diabetes, head injury, stroke, substance abuse

Table 3. The most common exposure histories for disease-modifying anti-rheumatic drugs (DMARDs) and their association with Parkinson's disease (PD) risk during the exposure assessment period before three-year lag in both PD cases and controls.

	Controls N=1571 n (%)	PD cases N=315 n (%)	Adjusted* OR (95% CI)
Sulfasalazine	165 (10.5)	32 (10.2)	reference
Chloroquine/hydroxychloroquine, methotrexate, and sulfasalazine	163 (10.4)	32 (10.2)	1.02 (0.58-1.79)
Chloroquine/hydroxychloroquine	109 (6.9)	13 (4.1)	0.64 (0.32-1.29)
Methotrexate and sulfasalazine	95 (6.1)	26 (8.3)	1.47 (0.82-2.65)
Methotrexate	81 (5.2)	19 (6.0)	1.19 (0.63-2.25)
Chloroquine/hydroxychloroquine and sulfasalazine	91 (5.8)	8 (2.5)	0.46 (0.20-1.06)
Gold preparations	80 (5.1)	14 (4.4)	0.95 (0.47-1.91)
Chloroquine/hydroxychloroquine and methotrexate	79 (5.0)	13 (4.1)	0.95 (0.46-1.94)

*Asthma or chronic obstructive pulmonary disease (COPD), cancer history, cardiovascular diseases, diabetes, head injury, stroke, substance abuse

Supplemental content

eTable 1. Definitions and classifications of rheumatoid arthritis.

	ICD code or classification number	**Measurement and data source**
Rheumatoid arthritis	Hospitalization: ICD-9: 714, 7140A, 7141A, 7143A, 7143B, 7143X	Diagnosed in the FCR 1987-1995
	Hospitalization or specialized healthcare outpatient visit: ICD-10: M05-M059, M06, M061	Hospitalizations 1996 onwards, specialized healthcare outpatient visits 1998 onwards
	Special reimbursement for medications: classification number 202 along with one of the abovementioned ICD-9 or ICD-10 codes	Reimbursement since 1972 in the SRR
	Hospitalization: ICD-8 codes 71200, 71210, 71238 and 71239 were used as additional information to acquire the earliest possible date for rheumatoid arthritis diagnosis provided that one of the abovementioned ICD-9 or ICD-10 codes was also present	Diagnosed in the FCR 1972-1986

Abbreviations: FCR=Finnish Care Register for Health Care; ICD=International Classification of Diseases; PR=Prescription Register; SRR=Special Reimbursement Register

eTable 2. Definition of exposure to disease-modifying anti-rheumatic drugs (DMARDs) and corticosteroids.

Drug substance or class	Drug substance	ATC code	Recorded in the Prescription register
Sulfasalazine		A07EC01	Since 1995
Methotrexate		L04AX03	Since 1995
Chlororoquine/	Chloroquine	P01BA01	1995-2003
hydroxychloroquine	Hydroxychloroquine	P01BA02	Since 1995
Gold preparations	Sodium aurothiomalate	M01CB01	Since 1995
	Auranofin	M01CB03	1995-2012
Immunosuppressants	Mycophenolic acid	L04AA06	Since 1998
	Leflunomide	L04AA13	Since 2000
	Ciclosporin	L04AD01	Since 1995
	Azathioprine	L04AX01	Since 1995
	bDMARDs:		
	Abatacept	L04AA24	Since 2013
	Etanercept	L04AB01	Since 2003
	Adalimumab	L04AB04	Since 2004
	Certolizumab pegol	L04AB05	Since 2010
	Golimumab	L04AB06	Since 2010
	Anakinra	L04AC03	Since 2004
Corticosteroids	Methylprednisolone	H02AB04	Since 1995
	Prednisolone	H02AB06	Since 1995
	Prednisone	H02AB07	Since 1995

Abbreviations: ATC=Anatomical Therapeutic Chemical; bDMARDs=biological disease-modifying anti-rheumatic drugs

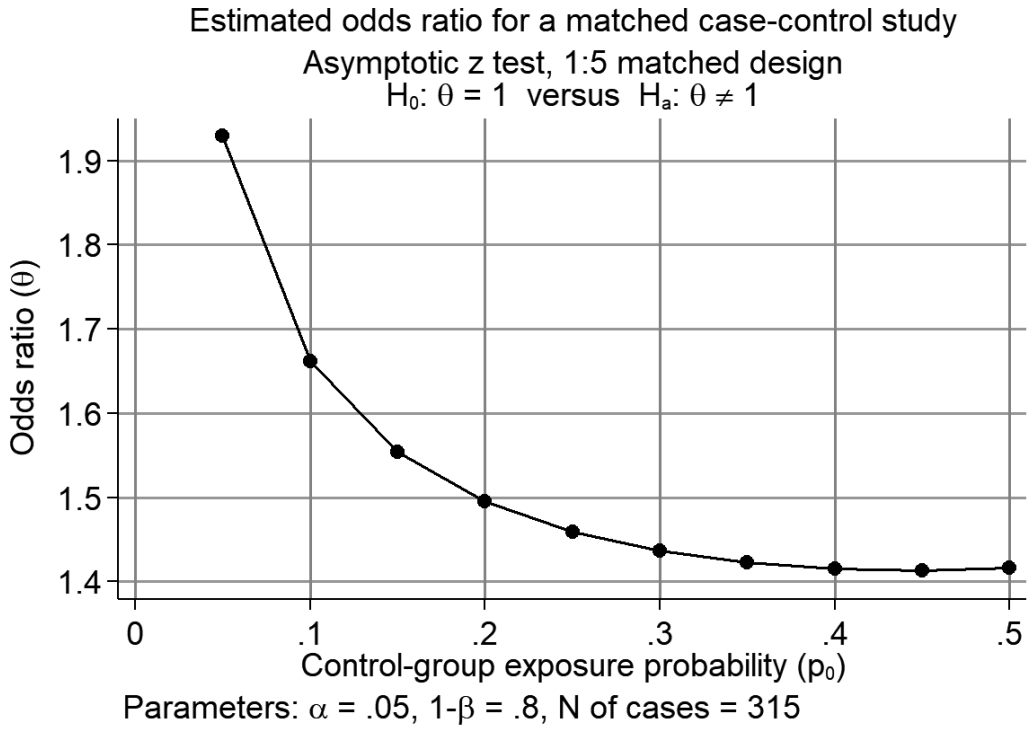
eTable 3. Definitions and classifications of covariates.

Covariate	**ATC code, ICD code or classification number**	**Measurement and data source**
Asthma or COPD	Hospitalization ICD-8: 493 ICD-9: 493, 4912A, 4960A ICD-10: J44–J46 Special reimbursement for medications: classification number 203	Diagnosed in the FCR ICD-8: 1972-1986 ICD-9: 1987-1995 ICD-10: hospitalizations 1996 onwards, specialized healthcare outpatient visits 1998 onwards Reimbursement since 1972 in the SRR
Cancer history	Hospitalization ICD-10 code from IARC CRG Tools: C00-C97	Diagnosed since 1972 in the Cancer Register
Cardiovascular diseases	Special reimbursement for medications: classification numbers 201, 205, 206, 207, 213, 280	Reimbursement since 1972 in the SRR
Diabetes	Hospitalization ICD-8: 250, 25101 ICD-9: 250, 2510, 2518 ICD-10: E10–E14	Diagnosed in the FCR ICD-8: 1972-1986 ICD-9: 1987-1995 ICD-10: hospitalizations 1996 onwards, specialized healthcare outpatient visits 1998 onwards

	Special reimbursement for medications: classification number 103	Reimbursement since 1972 in the SRR
Head injury	Hospitalization ICD-8: 800–804, 830, 850–854, 870–873, 904, 906, 910, 920, 921, 950, 951 ICD-9: 800–803,830, 8480, 850–854, 870–873, 918, 920, 921, 9250, 9251, 950, 951, 9590 ICD-10: S00–S09	Diagnosed in the FCR ICD-8: 1972-1986 ICD-9: 1987-1995 ICD-10: hospitalizations 1996 onwards, specialized healthcare outpatient visits 1998 onwards
Stroke	Hospitalization ICD-8: 430-434 ICD-9: 430–432 ICD-10: I60-I64	Diagnosed in the FCR ICD-8: 1972-1986 ICD-9: 1987-1995 ICD-10: hospitalizations 1996 onwards, specialized healthcare outpatient visits 1998 onwards
Substance abuse	Hospitalization ICD-8: 291, 3031, 3032, 3039, 980 ICD-9: 291, 292, 303-305, 980, 3575, 3594, 4255, 5353, 7903, 5710A, 5711A, 5712A, 5713A, 5713X, 5771C, 5771D	Diagnosed in the FCR ICD-8: 1972-1986 ICD-9: 1987-1995

	ICD-10: F10-F19, G31.2, G62.1, G72.1, I42.6, K29.2, K70, K86.0, R78.0, T51.0, T51.1, T51.9, X45 Reason for admission: codes 33, 71–75 Medication used in alcohol or opioid dependence (ATC code: N07BB, N07BC)	ICD-10: hospitalizations 1996 onwards, specialized healthcare outpatient visits 1998 onwards Since 1993 Medication use since 1995 in the PR

Abbreviations: ATC=Anatomical Therapeutic Chemical; COPD=chronic obstructive pulmonary disease; FCR=Finnish Care Register for Health Care; IARC CRG=International Agency for Research on Cancer Cancer Collaborative Research Group; ICD=International Classification of Diseases; PD=Parkinson's disease; PR=Prescription Register; SRR=Special Reimbursement Register



eFigure 1: Detectable odds ratios with 80% power, alpha=0.05 for our case-control study of 315 cases and five matched controls per case with exposure level of controls ranging between 5-50%. Up to seven controls per case were included but the average number of controls per case was five.

III

β2-adrenoceptor agonists in asthma or chronic obstructive pulmonary disease and risk of Parkinson's disease: nested case-control study

Paakinaho, A., Tiihonen M., Koskela H., Koponen, M., Tiihonen J., Hartikainen, S. and Tolppanen, A.-M.

Clinical Epidemiology 15: 695-705, 2023

Clinical Epidemiology

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

β2-Adrenoceptor Agonists in Asthma or Chronic Obstructive Pulmonary Disease and Risk of Parkinson's Disease: Nested Case-Control Study

Anne Paakinaho[1], Miia Tiihonen[1], Heikki Koskela[2,3], Marjaana Koponen[1,4], Jari Tiihonen[5,6], Sirpa Hartikainen[1], Anna-Maija Tolppanen[1]

[1]School of Pharmacy, Faculty of Health Sciences, University of Eastern Finland, Kuopio, Finland; [2]Unit for Medicine and Clinical Research, Pulmonary Division, Kuopio University Hospital, Kuopio, Finland; [3]School of Medicine, Faculty of Health Sciences, University of Eastern Finland, Kuopio, Finland; [4]Centre for Medicine Use and Safety, Faculty of Pharmacy and Pharmaceutical Sciences, Monash University, Parkville, Victoria, Australia; [5]Department of Forensic Psychiatry, University of Eastern Finland, Niuvanniemi Hospital, Kuopio, Finland; [6]Department of Clinical Neuroscience, Karolinska Institutet, and Center for Psychiatry Research, Stockholm City Council, Stockholm, Sweden

Correspondence: Anne Paakinaho, School of Pharmacy, Faculty of Health Sciences, University of Eastern Finland, P.O. Box 1627, Kuopio, FI-70211, Finland, Tel +358 405408490, Email anne.paakinaho@uef.fi

Introduction: Although β2-adrenoceptor (β2AR) agonists have been associated with a lower risk of Parkinson's disease (PD), the findings are inconclusive and may reflect confounding by indication. We studied the association between inhaled β2AR agonists and risk of PD in persons with asthma or chronic obstructive pulmonary disease (COPD).

Methods: The nested case-control study was conducted within a register-based Finnish Parkinson's disease study (FINPARK) and included 1406 clinically verified PD cases diagnosed during 1999–2015, who also had asthma/COPD >3 years before PD. PD cases were matched with up to seven controls by age, sex, duration of asthma/COPD, pulmonary diagnosis, and region (N = 8630). Cumulative and average annual exposure to short- and long-acting β2AR agonists before a 3-year lag period was assessed with quartiles of defined daily doses (DDDs). Adjusted odds ratios (aORs) were calculated with 95% confidence intervals (CIs) using conditional logistic regression.

Results: Cumulative exposure to either short- or long-acting β2AR agonists was not associated with a risk of PD. With average annual exposure, a decreased risk was observed only for the highest quartile of long-acting β2AR agonists (aOR 0.75; 95% CI 0.58–0.97). In the stratified analysis the lowest risk estimates were observed among those with both asthma and COPD diagnoses. The suggestion of an inverse association was seen for the highest quartile of long-acting β2AR agonists in asthma.

Discussion: Higher levels of exposure to β2AR agonists were not consistently associated with a reduced risk of PD. The inverse association in the highest category of average annual exposure to long-acting β2AR agonists may be explained by unmeasured confounding, such as disease severity or smoking.

Keywords: Parkinson disease, adrenergic beta-2 receptor agonists, asthma, chronic obstructive pulmonary disease, risk factors

Introduction

Better understanding of risk factors for Parkinson's disease (PD) could help in elucidating the causes and disease process of PD. Medications targeting the β2-adrenoceptor (β2AR) have been studied in this context, but despite the mechanistic evidence,[1] the results from observational epidemiological studies are not as conclusive.[2–4]

The β2ARs can regulate α-synuclein gene (SNCA) expression by epigenetic mechanisms and β2AR agonists (eg salbutamol) decreased, and conversely β2AR antagonists increased SNCA expression in different experimental models.[1] After the initial epidemiological study that showed a decreased risk of PD for salbutamol users,[1] other epidemiological studies have investigated the association between β2AR agonists and risk of PD.[2,4–10] Also recently β2AR agonist combination products (specifically, formoterol combined with budesonide) were associated with a decreased risk of PD in a study that aimed to identify candidates for repurposing with a machine learning-based signal detection approach.[11]

Received: 31 January 2023
Accepted: 22 May 2023
Published: 12 June 2023

Due to inconsistent findings in previous studies, the implied protective effect of β2AR agonists on PD development is being debated.[3,12] The inconsistency in previous literature might be due to differences in study populations and settings. Most of the previous studies have simultaneously investigated the associations of β2AR agonists and antagonists, and due to different indications for β2AR antagonists, these studies were not restricted to people with pulmonary diseases.[2,4,7–9] As β2AR agonists are used to treat asthma and chronic obstructive pulmonary disease (COPD), the lower risk of PD among β2AR agonist users might be explained by confounding by indication. Asthma and COPD are chronic diseases with an inflammatory process involvement, and airway obstruction as hallmark, although in asthma the obstruction is reversible and in COPD mainly irreversible.[13] Smoking has been suggested as one possible explanation for the protective association for β2AR agonists.[3] Smoking has been linked to a lower risk of PD[14] and it is the strongest risk factor for COPD for which β2AR agonists are frequently prescribed.[15]

Confounding by indication could be minimized by restricting a study to persons with asthma or COPD. This could also reduce the influence of smoking, especially when restricting to COPD, because smoking is not directly recorded in the register data. However, there are only two previous indication-restricted studies, both conducted with a nested case-control design. A study restricted to persons with COPD did not demonstrate an association between β2AR agonist use and risk of PD.[5] In another study of persons with asthma or COPD with exposure to β2AR agonists measured as months exposed, an increasing use of short-acting but not long-acting β2AR agonists were associated with a lower risk of PD.[6]

We evaluated the association between inhaled β2AR agonists and risk of PD in a nationwide nested case-control study restricted to people with asthma or COPD. We also investigated whether there is a dose-response relationship between short- and long-acting β2AR agonists and risk of PD. To control for reverse causality (for example, PD cases having higher contact with prescribers due to prodromal symptoms and consequently higher likelihood for medication changes), exposure that had occurred at least three years before the outcome was considered.

Methods

Study Population and Data Sources

The Finnish Parkinson's disease study (FINPARK) is a nested case-control study within the population of Finland. FINPARK includes 22,189 community-dwelling residents of Finland who received special reimbursement for PD drugs during 1996–2015. These persons with clinically verified PD were identified from the Special Reimbursement Register that contains information on entitlements to higher reimbursements for drugs due to chronic diseases. Special reimbursement for PD drugs is granted if predefined criteria for PD diagnosis are fulfilled and diagnoses must be confirmed by a neurologist. Initially, FINPARK included 29,942 persons with reimbursement for PD drugs, but 25.9% of them were excluded to increase the validity of PD diagnosis. Exclusions have been described in detail earlier,[16] and the proportion of excluded persons corresponds to the estimated proportion of people with a false PD diagnosis.[17,18] Up to seven age, sex, and region of residence matched comparison persons without PD (N = 148 009) were identified for cases from the Social Insurance Institution database.

Personal identification numbers enable linkage across nationwide Finnish registers. Data on chronic diseases is extracted from the Special Reimbursement Register and reimbursed prescription drugs from the Prescription Register which are both maintained by the Social Insurance Institution of Finland. Information on hospitalizations was obtained from the Care Register for Health Care maintained by the Finnish Institute for Health and Welfare. Cancer history was extracted from the Finnish Cancer Registry maintained by the Cancer Society of Finland and occupational social class from Statistics Finland.

Identification of Cases and Controls for This Study

Cases who were diagnosed with PD during 1999–2015 and diagnosed with asthma or COPD >3 years before PD diagnosis were selected (N = 1422). Cases diagnosed in 1996–1998 were excluded because Prescription Register data are available since 1995, and a 3-year lag was applied in drug exposure assessment. Thus, the drug exposure assessment period ranged between 1–17 years. The lag period of three years stems from a previous study on the FINPARK cohort showing that the incidence of muscle relaxant use, a sign of prodromal motor symptoms, began to increase among PD cases already three years before the diagnosis.[19]

Formation of the study population is described in Figure 1. Asthma and COPD were defined from the Finnish Care Register for Health Care (1972–2012) using ICD-10, ICD-9, and ICD-8 codes and from the Special Reimbursement

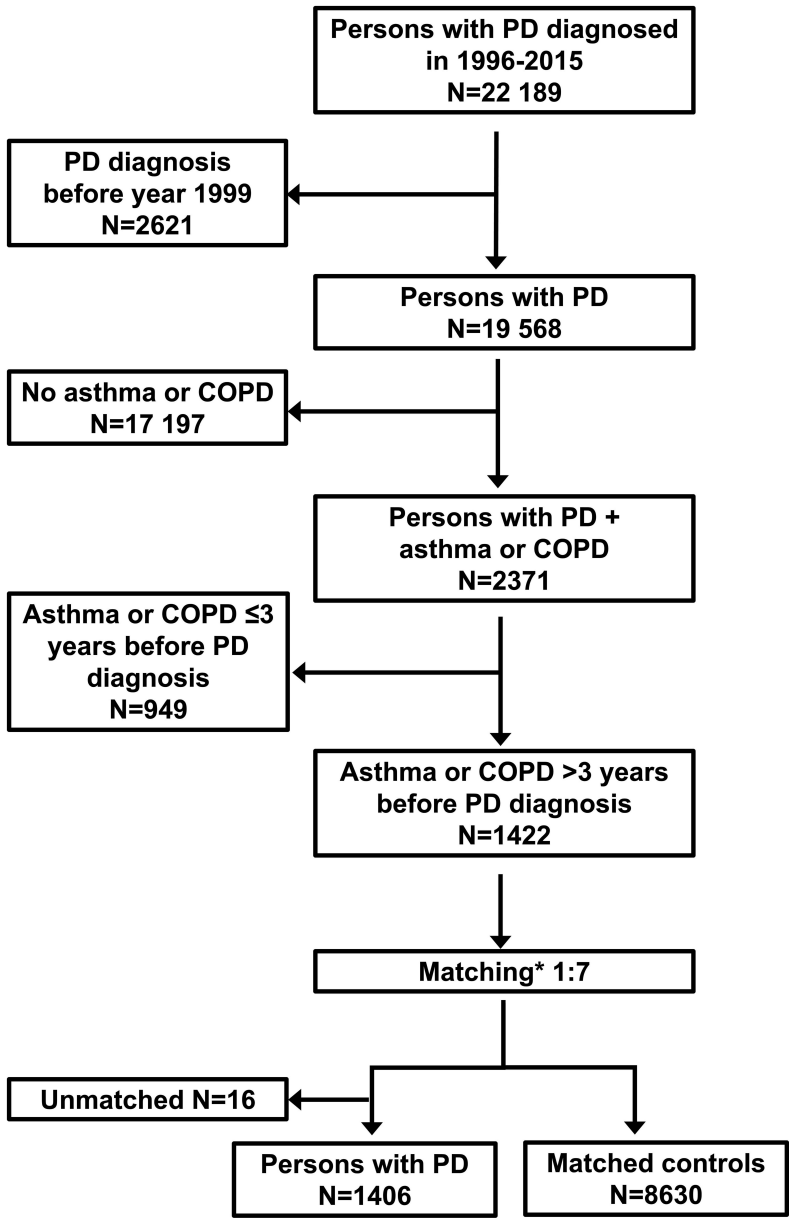


Figure 1 Flowchart of the formation of PD cases and their matched controls. *Age ± 2 years, sex, pulmonary diagnosis (asthma, COPD or both), time since asthma/COPD diagnosis ± 3 years, university hospital district.
Abbreviations: COPD, chronic obstructive pulmonary disease; PD, Parkinson's disease.

Register (1972–2012) using ICD-10 and ICD-9 codes (Supplementary Table 1). The diagnosis date for asthma or COPD was determined either as the earliest date for the hospitalization or specialized healthcare outpatient visit, or as the date for the entitlement to reimbursement for drugs that are used in the treatment of asthma or COPD, depending on which occurred first.

Each PD case (N = 1422) was matched up to seven controls who were diagnosed with asthma or COPD but had no PD diagnosis from the controls of the entire FINPARK study. Controls were matched on the date of PD diagnosis for the case (index date). Controls were matched according to age (± 2 years) on index date, same sex, and pulmonary diagnosis type (asthma, COPD, or both), time since asthma or COPD diagnosis on index date (± 3 years) and university hospital district, which could be the same or neighboring district. The exclusion criteria for cases and controls were the same except that the controls were not allowed to have dementia in PD (ICD-10 code F02.3). Cases (N=16) that no controls were found were excluded and the final study population comprised of 1406 PD cases and 8630 matched controls.

Drug Exposure

Exposure to β2AR agonists since 1995 was obtained from the Prescription Register. The Prescription Register covers all reimbursed prescription drug purchases and drugs used in the hospitals are not included. Drugs are categorized according to Anatomical Therapeutic Chemical (ATC) classification codes and for each drug the register includes information such as the dispensing date, number of packages and defined daily dose (DDD) per purchase. The DDD is the assumed average maintenance dose per day for a drug used for its main indication for adults.[20]

Use of β2AR agonists were defined with ATC codes and were categorized as short-acting (salbutamol, terbutaline, fenoterol) and long-acting β2AR agonists (salmeterol, formoterol, indacaterol, olodaterol, and vilanterol) (Supplementary Table 2). The combinations of β2AR agonists with corticosteroids and anticholinergics were included. Additionally, use of inhaled corticosteroids and anticholinergics were extracted separately (Supplementary Table 2).

Exposure was extracted until the beginning of the 3-year lag period and categorized as use/no use before the 3-year lag. The earliest date of purchase was determined. The lag period was applied to minimize protopathic bias ie the likelihood that prodromal symptoms or diagnostic process of PD could affect drug exposure. After applying the 3-year lag period, possible drug exposure assessment period was 10.8 years on average.

The dose-response analyses were restricted to those who used β2AR agonists at least 3 years before index date. Due to matched design, those PD cases and controls who were unmatched after the exclusion of nonusers were also excluded. Cumulative exposure was calculated as cumulative sum of DDDs. We estimated in how many distinct years in relation to index date the user had carried out purchases. Cumulative DDDs were divided by the sum of years with purchase to get an average exposure per year (later briefly annual exposure). Continuous variables, cumulative DDDs, and annual exposure were categorized into quartiles in the main analyses and into tertiles in sensitivity analyses. These analyses were performed for short- and long-acting β2AR agonists separately and on any β2AR agonist level when use of either short- and/or long-acting β2AR agonists was considered.

Confounders

History of comorbid conditions comprised of cardiovascular diseases, diabetes, stroke, substance abuse and traumatic brain injury and were identified from the Finnish Care Register for Health Care, the Special Reimbursement Register or the Prescription Register. Additionally, history of cancer was obtained from the Cancer Registry. All comorbid conditions were measured until the start of the 3-year lag period and data sources, specific codes, coding systems, and time periods are described in more detail in Supplementary Table 3. Information on the highest occupational socioeconomic position in 1972–1994, was derived from Statistics Finland data and grouped according to classification by Statistics Finland. Students, long-term unemployed, other positions not elsewhere classified, socioeconomic status unknown or missing where classified into the ‘Others’ class.

Statistical Analyses

Characteristics of PD cases and controls and different exposure groups were compared with a Chi-Square test for categorical variables. *T*-test was applied for continuous variables that were normally distributed and Mann–Whitney *U*-test for nonnormally distributed variables. Use of inhaled β2AR agonists, corticosteroids and anticholinergics was compared between cases and controls. The associations between use of β2AR agonists and PD were investigated with conditional logistic regression due to the matched design. The analyses were adjusted with potential confounders. In addition, sensitivity analyses with additional adjustment for inhaled corticosteroids and anticholinergics were performed.

For categorical variables cumulative DDDs and annual exposure, the lowest quantile was used as reference. To evaluate whether the statistically significant associations were modified by pulmonary diagnoses, a model with exposure*pulmonary diagnosis interaction term was fitted and if there was evidence of modification (P for interaction <0.1), stratified analyses according to pulmonary diagnosis were performed. The Kruskal–Wallis test was applied to estimate differences in continuous variables, cumulative DDD, and annual exposure between pulmonary diagnosis types. Statistical analyses were conducted with SAS 9.4.

Results

Characteristics of 1406 PD cases and 8630 controls are presented in Table 1. Mean age was 73 years ranging from 33 to 95 years in the study population and 51% of both cases and controls were men. The median duration of asthma/COPD on index date was 12.4 years for controls and 12.9 for cases. The majority of the cases and controls had only asthma

Table 1 Description of PD Cases and Controls with Asthma/COPD

	Controls	PD Cases	*P*[a]
	N = 8630	**N = 1406**	
Age on index date, years; mean (SD)	72.9 (8.2)	72.7 (8.8)	0.39[b]
Sex; n (%)			0.74
Men	4366 (50.6)	718 (51.1)	
Women	4264 (49.4)	688 (48.9)	
Duration of asthma/COPD on index date; median (IQR)	12.4 (7.2–19.9)	12.9 (7.3–20.7)	0.14[c]
Pulmonary diagnosis type; n (%)			0.13
Asthma	6633 (76.9)	1047 (74.5)	
Asthma and COPD	1236 (14.3)	226 (16.1)	
COPD	761 (8.8)	133 (9.5)	
Covariates; n (%)			
Cardiovascular diseases	4093 (47.4)	674 (47.9)	0.72
Diabetes	973 (11.3)	163 (11.6)	0.73
Cancer history	814 (9.4)	107 (7.6)	0.028
Stroke	379 (4.4)	67 (4.8)	0.53
Substance abuse	323 (3.7)	54 (3.8)	0.86
Traumatic brain injury	207 (2.4)	26 (1.9)	0.20
Socioeconomic position; n (%)			0.17
Manual workers	2669 (30.9)	440 (31.3)	
Self-employed	2299 (26.6)	351 (25.0)	
Lower-level employees with administrative and clerical occupations	2057 (23.8)	326 (23.2)	
Upper-level employees with administrative, managerial, professional and related occupations	1121 (13.0)	188 (13.4)	
Pensioners	432 (5.0)	93 (6.6)	
Others	52 (0.6)	8 (0.6)	
β2AR agonists; n (%)	7444 (86.3)	1225 (87.1)	0.38
Short-acting β2AR agonists; n (%)	7176 (83.2)	1183 (84.1)	0.36
Salbutamol	5556 (64.4)	926 (65.9)	0.28
Terbutaline	2052 (23.8)	317 (22.6)	0.31
Fenoterol	1233 (14.3)	211 (15.0)	0.48
Long-acting β2AR agonists; n (%)	4179 (48.4)	683 (48.6)	0.92
Salmeterol	2991 (34.7)	479 (34.1)	0.67
Formoterol	1943 (22.5)	319 (22.7)	0.88
Indacaterol	8 (0.1)	-	
Olodaterol	-	-	
Vilanterol	-	-	

Notes: Covariates and inhaled β2AR agonist exposure are measured before the 3-year lag period, socioeconomic position in 1972–1994. Index date is the date of PD diagnosis or corresponding matching date for controls. [a]Chi-Square test, [b]*t*-test, [c]Mann–Whitney *U*-test.

Abbreviations: β2AR, β2-adrenoceptor; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; PD, Parkinson's disease; SD, standard deviation.

(>74%), approximately 15% had both asthma and COPD and less than 10% had only COPD. The history of comorbid conditions before the 3-year lag period were similar between cases and controls, except for cancer history which prevalence was higher among controls. Cardiovascular diseases were the most common comorbidities.

Distribution of inhaled β2AR agonist exposure was similar between cases and controls (Table 1). Over 83% had purchased short-acting and 48% long-acting β2AR agonists. Neither short- nor long-acting β2AR agonists were associated with risk of PD when any use was compared to nonuse before the 3-year lag (adjusted odds ratio (aOR) 1.13; 95% CI 0.95–1.33 and 1.01; 0.89–1.14, respectively). Exposure to inhaled corticosteroids and anticholinergics was comparable between cases and controls (Supplementary Table 4), and additional adjustment for them did not affect the association of any short- or long-acting β2AR agonist use before the 3-year lag in sensitivity analyses (1.12; 95% CI 0.93–1.36 and 0.99; 0.87–1.13, respectively).

Altogether, 7376 users of short-acting, 2889 users of long-acting and 7851 users of any β2AR agonists were included in the dose-response analyses. Cumulative DDDs were not associated with risk of PD in any of the analyses (Table 2).

Table 2 Dose-Response Associations Between Use of Inhaled β2AR Agonists and PD

Short-acting β2AR agonists	**Controls N = 6199 n (%)**	**PD cases N = 1177 n (%)**	**OR (95% CI)**	**Adjusted OR (95% CI)[a]**
Cumulative DDD				
7–75 DDD	1583 (25.5)	303 (25.7)	Reference	Reference
78–223 DDD	1485 (24.0)	302 (25.7)	1.07 (0.90–1.28)	1.06 (0.89–1.27)
225–633 DDD	1562 (25.2)	299 (25.4)	0.99 (0.82–1.18)	0.98 (0.82–1.17)
635–14016 DDD	1569 (25.3)	273 (23.2)	0.84 (0.70–1.02)	0.84 (0.69–1.02)
Annual exposure				
7–33 DDD/year	1591 (25.7)	305 (25.9)	Reference	Reference
34–57 DDD/year	1505 (24.3)	289 (24.6)	1.01 (0.85–1.21)	1.01 (0.85–1.20)
58–113 DDD/year	1559 (25.2)	282 (24.0)	0.94 (0.79–1.13)	0.93 (0.78–1.12)
114–1533 DDD/year	1544 (24.9)	301 (25.6)	0.92 (0.76–1.11)	0.91 (0.75–1.10)
Long-acting β2AR agonists	**Controls N = 2240 n (%)**	**PD cases N = 649 n (%)**	**OR (95% CI)**	**Adjusted OR (95% CI)[a]**
Cumulative DDD				
15–240 DDD	544 (24.3)	177 (27.3)	Reference	Reference
255–900 DDD	555 (24.8)	167 (25.7)	0.93 (0.73–1.19)	0.94 (0.73–1.21)
915–2100 DDD	574 (25.6)	154 (23.7)	0.88 (0.68–1.14)	0.89 (0.69–1.16)
2115–11010 DDD	567 (25.3)	151 (23.3)	0.88 (0.67–1.15)	0.88 (0.67–1.16)
Annual exposure				
15–105 DDD/year	549 (24.5)	180 (27.7)	Reference	Reference
107–210 DDD/year	567 (25.3)	170 (26.2)	0.90 (0.70–1.16)	0.91 (0.71–1.17)
212–310 DDD/year	541 (24.2)	160 (24.7)	0.93 (0.72–1.19)	0.94 (0.73–1.21)
311–1032 DDD/year	583 (26.0)	139 (21.4)	0.74 (0.57–0.97)	0.75 (0.58–0.97)
Any β2AR agonist	**Controls N = 6632 n (%)**	**PD cases N = 1219 n (%)**	**OR (95% CI)**	**Adjusted OR (95% CI)[a]**
Cumulative DDD				
6–148 DDD	1615 (24.4)	293 (24.0)	Reference	Reference
150–555 DDD	1678 (25.3)	337 (27.7)	1.12 (0.94–1.33)	1.11 (0.93–1.32)
560–1848 DDD	1648 (24.9)	315 (25.8)	1.06 (0.89–1.27)	1.06 (0.89–1.27)
1850–15246 DDD	1691 (25.5)	274 (22.5)	0.85 (0.70–1.03)	0.85 (0.70–1.03)
Annual exposure				
6–49 DDD/year	1524 (23.0)	263 (21.6)	Reference	Reference
50–120 DDD/year	1793 (27.0)	361 (29.6)	1.17 (0.98–1.39)	1.16 (0.97–1.38)
121–259 DDD/year	1632 (24.6)	312 (25.6)	1.11 (0.92–1.33)	1.11 (0.92–1.33)
260–1691 DDD/year	1683 (25.4)	283 (23.2)	0.92 (0.76–1.11)	0.92 (0.76–1.11)

Notes: [a]Cancer history, cardiovascular diseases, diabetes, socioeconomic position, stroke, substance abuse and traumatic brain injury.
Abbreviations: β2AR, β2-adrenoceptor; CI, confidence interval; OR, odds ratio; PD, Parkinson's disease.

There was no association between annual exposure and risk of PD for short-acting β2AR agonists or for any β2AR agonists. The highest quartile for annual exposure for long-acting β2AR agonists was associated with a decreased risk of PD (aOR 0.75; 95% CI 0.58–0.97) (Table 2). The results of sensitivity analyses with tertile categorization were similar to main analyses, with narrower 95% CIs resulting from borderline association between the highest cumulative exposure to any β2AR agonist and lower risk of PD (aOR 0.85; 95% CI 0.72–1.00). In addition, the association of the highest tertile of annual exposure for long-acting β2AR agonists was weaker (aOR 0.82; 95% CI 0.65–1.02, Supplementary Table 5) than the association of the highest quartile in the main analysis. The results from sensitivity analysis with further adjustment with inhaled corticosteroids and anticholinergics for quartile categorization were similar to the main analysis (Supplementary Table 6).

There was evidence for different association per pulmonary diagnosis type in this dose-response analysis of annual exposure for long-acting β2AR agonists (P for interaction 0.07). The lowest aORs were observed among those with both asthma and COPD (N = 670) with the third quartile of annual exposure (aOR 0.48; 95% CI 0.27–0.87), but not the fourth quartile, being associated with a decreased risk of PD compared with the lowest quartile (Figure 2). For asthma (N = 2089), the highest quartile showed a slight protective association (aOR 0.74; 95% CI 0.55–1.01). No associations were seen among those with only COPD (N = 130). People with asthma and COPD had the highest annual exposure for long-acting β2AR agonists (median 240 DDD/year; interquartile range (IQR) 141–316) than asthma (median 200 DDD/year; IQR 99–309) and COPD (median 173 DDD/year; IQR 90–300), p<0.0001 (Table 3).

Discussion

Findings of this nested case-control study of people with asthma/COPD suggest that the use of inhaled β2AR agonists is not associated with risk of PD and higher cumulative exposure is not consistently associated with lower risk of developing PD. An association with a decreased risk was observed only for the highest quartile of annual exposure for long-acting β2AR agonists. This was modified by pulmonary diagnosis type, with the lowest aORs among those with both asthma and COPD diagnosis. This might suggest that regular and long-term use of long-acting β2AR agonists is

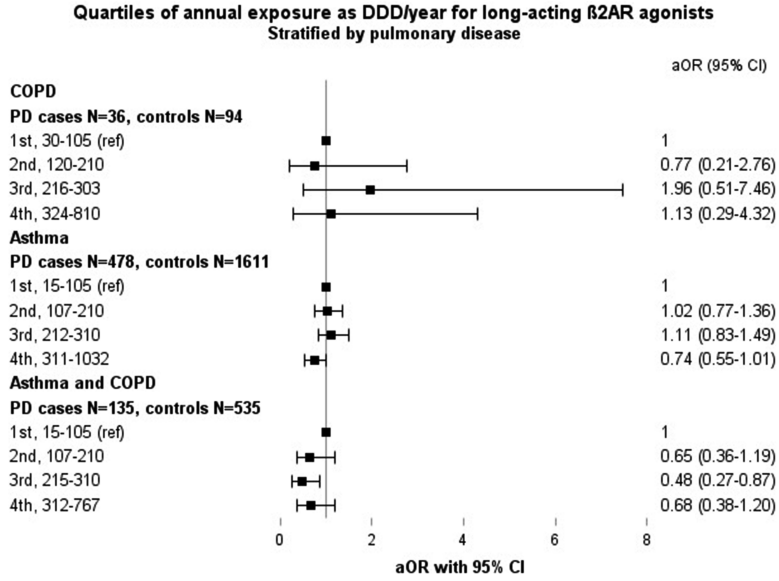


Figure 2 Stratified analysis across quartiles of average annual exposure for long-acting β2AR agonists by pulmonary disease. Adjusted with cancer history, cardiovascular diseases, diabetes, socioeconomic position, stroke, substance abuse and traumatic brain injury.

Abbreviations: β2AR, β2-adrenoceptor; aOR, adjusted odds ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease; DDD, defined daily dose; PD, Parkinson's disease.

Table 3 Comparison of Cumulative DDD and Average Annual Exposure (DDD/Year) for β2AR Agonists Between Different Pulmonary Diagnosis Types. Results are Reported as Median (IQR)

	Short-Acting β2AR Agonists			Long-Acting β2AR Agonists			Any β2AR Agonist		
	N	Cumulative DDD	Annual Exposure (DDD/Year)	N	Cumulative DDD	Annual Exposure (DDD/Year)	N	Cumulative DDD	Annual Exposure (DDD/Year)
COPD	417	125 (50–550)	50 (33–133)	130	360 (120–1200)	173 (90–300)	479	285 (67–1265)	100 (47–247)
Asthma	5761	200 (75–575)	50 (32–100)	2089	900 (240–2100)	200 (99–309)	6106	500 (143–1700)	104 (49–234)
Asthma and COPD	1198	350 (125–1040)	88 (49–194)	670	1140 (390–2310)	240 (141–316)	1266	1130 (350–2693)	225 (100–357)
***p*-value**		<0.0001	<0.0001		<0.0001	<0.0001		<0.0001	<0.0001

Abbreviations: β2AR, β2-adrenoceptor; COPD, chronic obstructive pulmonary disease; DDD, defined daily dose; IQR, interquartile range.

more common among those with more severe disease such as persons with both asthma and COPD, and the protective association might be confounded by lifestyle factors such as smoking.

Although direct comparisons to earlier studies are challenging due to differences in methods and study populations, our findings are supportive of those from a nested case-control study restricted to persons with COPD. In that study, the use of short- or long-acting β2AR agonists was not associated with risk of PD.[5] The exposure was assessed every six months for a 2-year window and categorized into regular, irregular use and no use. After applying a 2- or 3-year lag period, neither regular nor irregular use was associated with risk of PD compared to nonuse.[5] Another nested case-control study of persons with asthma/COPD studied short- and long-acting β2AR agonists separately, and reported an association between short-acting β2AR agonist and lower risk of PD (OR 0.90; 95% CI 0.86–0.96 per additional month of exposure),[6] while we did not observe any association with short-acting β2AR agonist use. Additionally, a cohort study which investigated the association between asthma and risk of subsequent PD, reported no association for inhaled β2AR agonists compared to persons without asthma,[21] a result similar to our findings.

We did not observe a consistent protective association in the dose-response relationship analyses. Association was observed only for long-acting β2AR agonists in annual exposure analysis. Previous dose-response studies have mostly focused on salbutamol in study populations not restricted on asthma/COPD,[1,2] which complicates the comparison. Also, follow-up and exposure assessment periods are not directly comparable to our study. Only one study reported dose-response results for long-acting β2AR agonist formoterol comparing average daily dose quartiles to nonuse and quartiles were associated with a decreased risk of PD except for the lowest quartile.[4] In that same study, salbutamol average daily dose quartiles were associated with a decreased risk except for the highest quartile which was no longer associated with risk of PD compared to nonuse. As for salbutamol, findings from other two dose-response studies are varying.[1,2] In a previous cohort study, the second and third tertile of cumulative DDDs for salbutamol (including both inhaled and systemic) showed protective association for risk of PD compared to nonuse.[1] Categorization of cumulative DDDs in that study (<60, 60 to 180, ≥180 DDDs) are not comparable with ours since we had a longer exposure assessment period (10.8 years on average) compared to their maximum of 4 years. A case-control study[2] used similar categorization as previously described[1] but used the lowest tertile (<60 DDDs) as reference. No dose-response associations for inhaled salbutamol users overall or among smokers were found. In summary, higher cumulative exposure has not been consistently protective in previous studies when not restricted on asthma/COPD.

There was evidence for differential association between annual exposure to long-acting β2AR agonists and risk of PD per pulmonary diagnosis type. Strongest aORs were observed in those with both asthma and COPD diagnoses and a lower risk of PD was observed only in the third quartile. Even though the confidence intervals in the highest quartile overlapped 1, point estimate was suggestive of decreased risk. This kind of finding might be due to more severe and

complex pulmonary condition that we could not take into account in the analyses as this information is not recorded in registers. However, as was seen in our data, those with both asthma and COPD diagnoses were exposed to the highest amount of β2AR agonists compared to those with asthma or COPD alone. Thus, use of β2AR agonists can reflect the severity of the pulmonary disease. This group with both asthma and COPD diagnoses can resemble persons with Asthma–COPD Overlap Syndrome (ACOS). ACOS is a heterogeneous condition characterized by persistent airflow limitation[22] and can occur particularly in smokers and older adults.[23] Persons with ACOS can have more symptoms and exacerbations than asthma and COPD alone.[24]

Protective association could be confounded by smoking as protective effect of smoking against PD is well-known.[14] The role of smoking on the development of PD in epidemiological studies on β2AR agonists has been speculated previously.[2,3,7] According to a case-control study, long-term use of β2AR agonists was associated with a lower risk of PD compared to nonuse, but since markers of smoking were also associated with reduced risk of PD, authors interpreted the results to be indirectly mediated by smoking.[7] Number of smokers could be assumed to be highest among the COPD-only group, and higher among those with both asthma and COPD than asthma alone, since COPD is more likely smoking-related disease[25] than asthma.[26] The number of persons with COPD only was low in our study. Consequently, we had low power to detect associations but the point estimates in this group were not supportive of protective dose-response association. In the COPD group smoking may no longer be a significant confounder and mediate the association since the entire group is formed most likely by smokers and β2AR agonists might not be associated with risk of PD as also reported in a previous study restricted on people with COPD.[5] As for asthma, there was a suggestion of lower risk of PD in the highest exposure quartile, although there was otherwise no indication for dose-dependent association in the asthma-only group. Among asthmatics, smoking has been associated with increased asthma severity[26] and worse asthma control,[27] which could result in increased need of β2AR agonists, thus, the protective association in the highest exposure category could be indirectly mediated by smoking. The same phenomenon may explain the findings in the group with both asthma and COPD.

There are several strengths in our study. We were able to restrict the study population on asthma/COPD due to a large nationwide register data with a long follow-up period thus controlling for confounding by indication. In addition, we could have a 3-year lag period in exposure assessment. By applying a lag-period we could ascertain that drug exposure has happened before PD diagnosis and minimize reverse causality ie the likelihood of initiation or discontinuation of drugs due to prodromal symptoms of PD. We were able to account for multiple confounding factors even though we lacked information on smoking.

In Finland, diagnosis of asthma is based on patient history and clinical examination and objective evidence of reversible airway obstruction.[28] Diagnosis of COPD is based on relevant exposure history, symptoms and on the presence of fixed airway obstruction in spirometry.[29] One explanation for low prevalence of COPD in our study population can be an underdiagnosis of COPD in Finland.[30]

The register-based approach poses some limitations. Exposure for inhaled β2AR agonists defined from registers either as estimated duration of use from prescriptions filled or as DDDs are not necessarily exact as actual use and adherence is unknown. Especially in asthma, short-acting β2AR agonists can be used as as-needed rescue medications[31] and therefore a new inhaler can be purchased due to expiration of the previous one or due to stockpiling. Persons with persistent respiratory symptoms might purchase more frequently and use higher DDDs. In dose-response analyses the lowest exposure category was used as reference instead of nonusers for less biased comparison. For example, disease severity can differ between users vs nonusers regardless of the initial restriction to asthma/COPD. We did not have information on disease severity, but we matched cases and controls by duration of asthma/COPD.

In conclusion, inhaled β2AR agonists were not associated with a risk of PD among persons with asthma/COPD. Findings from dose-response analyses suggest that higher levels of exposure to β2AR agonists are not consistently associated with reduced risk of PD among persons with asthma/COPD. The protective association in the highest category of annual exposure to long-acting β2AR agonists may be explained by unmeasured confounding such as disease severity or smoking.

Data Sharing Statement

The datasets generated and/or analysed during the current study are not publicly available due to restrictions by the register maintainers and Finnish legislation but are available from the corresponding author upon reasonable request and with permission of the register maintainers.

Ethics Approval and Informed Consent

Register maintainers have approved the FINPARK study plan. Data were pseudonymized before submission to the research team and study participants were not contacted. Therefore, according to Finnish legislation (including Personal Data Act 23/1999, Act on the Openness of Government Activities 621/1999 and Act on the Secondary Use of Health and Social Data 552/2019, and previous Act on the National Healthcare registers [no official English translation as this is not available] 556/1989), the study has been granted an exemption from requiring ethics approval or informed consent.

Acknowledgments

This paper was presented at the 18th Congress of the European Geriatric Medicine Society as online poster with interim findings. The poster's abstract was published in Abstracts of the 18th Congress of the European Geriatric Medicine Society. Eur Geriatr Med 13 (Suppl 1), 1–439 (2022). https://doi.org/10.1007/s41999-022-00711-8. An oral presentation of this paper with interim findings was given at the 38th International Conference on Pharmacoepidemiology & Therapeutic Risk Management and at the 14th annual Nordic Pharmacoepidemiological Network meeting in 2022.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This study was funded by the Michael J Fox Foundation for Parkinson's research (grant MJFF-008834 to AMT, which paid salary for AP).

Disclosure

AP reports grant from the Finnish Parkinson Foundation and The Michael J. Fox Foundation for Parkinson's Research. HK reports grants from Kuopio Area Respiratory Foundation and The Research Foundation of the Pulmonary Diseases and payment for lectures from Boehringer Ingelheim Ltd and MSD Ltd and Stock ownership of Orion Ltd, all outside the submitted work. JT reports grant from Janssen-Cilag paid to his employing institution, Karolinska Institutet. JT is also a consultant to HLS Therapeutics and WebMed Global and has received lecture fees from Janssen-Cilag and Otsuka; all outside of the submitted work. AMT reports grant from the Michael J Fox Foundation for Parkinson's research (grant MJFF-008834 which paid salary for AP) related to this manuscript. AMT also reports research grant from Amgen, paid through the institution she is employed at, outside of the submitted manuscript. SH has got lecture fees from Eisai Ltd. MT and MK have no conflicts of interest to declare for this work.

References

1. Mittal S, Bjørnevik K, Im DS, et al. β2-Adrenoreceptor is a regulator of the α-synuclein gene driving risk of Parkinson's disease. *Science*. 2017;357 (6354):891–898. doi:10.1126/science.aaf3934
2. Searles Nielsen S, Gross A, Camacho-Soto A, Willis AW, Racette BA. β2-adrenoreceptor medications and risk of Parkinson disease. *Ann Neurol*. 2018;84(5):683–693. doi:10.1002/ana.25341
3. Hopfner F, Höglinger GU, Kuhlenbäumer G, et al. β-adrenoreceptors and the risk of Parkinson's disease. *Lancet Neurol*. 2020;19(3):247–254.
4. Gronich N, Abernethy DR, Auriel E, Lavi I, Rennert G, Saliba W. β2-adrenoceptor agonists and antagonists and risk of Parkinson's disease. *Mov Disord off J Mov Disord Soc*. 2018;33(9):1465–1471. doi:10.1002/mds.108

5. Chen W, Sadatsafavi M, Tavakoli H, Samii A, Etminan M. Effects of β2-adrenergic agonists on risk of Parkinson's disease in COPD: a population-based study. *Pharmacotherapy*. 2020;40(5):408–415. doi:10.1002/phar.2383
6. Marras C, Pequeno P, Austin PC, et al. Beta agonists and progression of Parkinson's disease in older adults: a retrospective cohort study. *Mov Disord off J Mov Disord Soc*. 2020;35(7):1275–1277. doi:10.1002/mds.28085
7. Hopfner F, Wod M, Höglinger GU, et al. Use of β2-adrenoreceptor agonist and antagonist drugs and risk of Parkinson disease. *Neurology*. 2019;93 (2):e135–e142. doi:10.1212/WNL.0000000000007694
8. Giorgianni F, Ernst P, Dell'Aniello S, Suissa S, Renoux C. β2-agonists and the incidence of Parkinson disease. *Am J Epidemiol*. 2020;189 (8):801–810. doi:10.1093/aje/kwaa012
9. de Germay S, Conte C, Rascol O, Montastruc JL, Lapeyre-Mestre M. β-adrenoceptor drugs and Parkinson's Disease: a nationwide nested case-control study. *CNS Drugs*. 2020;34(7):763–772. doi:10.1007/s40263-020-00736-2
10. Belvisi D, Pellicciari R, Fabbrini A, et al. Risk factors of Parkinson disease: simultaneous assessment, interactions, and etiologic subtypes. *Neurology*. 2020;95(18):e2500–e2508. doi:10.1212/WNL.0000000000010813
11. Courtois É, Nguyen TTH, Fournier A, et al. Identifying protective drugs for Parkinson's disease in health-care databases using machine learning. *Mov Disord off J Mov Disord Soc*. 2022;37:2376–2385. doi:10.1002/mds.29205
12. Magistrelli L, Comi C. Beta2-adrenoceptor agonists in Parkinson's disease and other synucleinopathies. *J Neuroimmune Pharmacol off J Soc NeuroImmune Pharmacol*. 2020;15(1):74–81. doi:10.1007/s11481-018-09831-0
13. Barnes PJ. Immunology of asthma and chronic obstructive pulmonary disease. *Nat Rev Immunol*. 2008;8(3):183–192. doi:10.1038/nri2254
14. Hernán MA, Takkouche B, Caamaño-Isorna F, Gestal-Otero JJ. A meta-analysis of coffee drinking, cigarette smoking, and the risk of Parkinson's disease. *Ann Neurol*. 2002;52(3):276–284. doi:10.1002/ana.10277
15. Yawn BP, Mintz ML, Doherty DE. GOLD in practice: chronic obstructive pulmonary disease treatment and management in the primary care setting. *Int J Chron Obstruct Pulmon Dis*. 2021;16:289–299. doi:10.2147/COPD.S222664
16. Hentilä E, Tiihonen M, Taipale H, Hartikainen S, Tolppanen AM. Incidence of antidepressant use among community dwellers with and without Parkinson's disease - a nationwide cohort study. *BMC Geriatr*. 2021;21(1):202–206. doi:10.1186/s12877-021-02145-6
17. Joutsa J, Gardberg M, Röyttä M, Kaasinen V. Diagnostic accuracy of parkinsonism syndromes by general neurologists. *Parkinsonism Relat Disord*. 2014;20(8):840–844. doi:10.1016/j.parkreldis.2014.04.019
18. Rizzo G, Copetti M, Arcuti S, Martino D, Fontana A, Logroscino G. Accuracy of clinical diagnosis of Parkinson disease: a systematic review and meta-analysis. *Neurology*. 2016;86(6):566–576. doi:10.1212/WNL.0000000000002350
19. Paakinaho A, Karttunen N, Koponen M, et al. Incidence of muscle relaxant use in relation to diagnosis of Parkinson's disease. *Int J Clin Pharm*. 2020;42(2):336–340. doi:10.1007/s11096-020-01002-7
20. WHOCC. Definition and general considerations; 2022. Available from: https://www.whocc.no/ddd/definition_and_general_considera/. Accessed May 13, 2022.
21. Cheng CM, Wu YH, Tsai SJ, et al. Risk of developing Parkinson's disease among patients with asthma: a nationwide longitudinal study. *Allergy*. 2015;70(12):1605–1612. doi:10.1111/all.12758
22. GINA & GOLD. Diagnosis of diseases of chronic airflow limitation: asthma, COPD and Asthma-COPD Overlap Syndrome (ACOS) 2015; 2015. Available from: https://goldcopd.org/asthma-copd-asthma-copd-overlap-syndrome/. Accessed May 19, 2022.
23. Zeki AA, Schivo M, Chan A, Albertson TE, Louie S. The asthma-COPD overlap syndrome: a common clinical problem in the elderly. *J Allergy*. 2011;2011:1–10. doi:10.1155/2011/861926
24. Nielsen M, Bårnes CB, Ulrik CS. Clinical characteristics of the asthma-COPD overlap syndrome--a systematic review. *Int J Chron Obstruct Pulmon Dis*. 2015;10:1443–1454. doi:10.2147/COPD.S85363
25. Postma DS, Bush A, van den Berge M. Risk factors and early origins of chronic obstructive pulmonary disease. *Lancet*. 2015;385(9971):899–909. doi:10.1016/S0140-6736(14)60446-3
26. Siroux V, Pin I, Oryszczyn MP, Le Moual N, Kauffmann F. Relationships of active smoking to asthma and asthma severity in the EGEA study. *Eur Respir J*. 2000;15(3):470–477. doi:10.1034/j.1399-3003.2000.15.08.x
27. Polosa R, Thomson NC. Smoking and asthma: dangerous liaisons. *Eur Respir J*. 2013;41(3):716–726. doi:10.1183/09031936.00073312
28. Koskela HO, Hyva¨rinen L, Brannan JD, Chan HK, Anderson SD. Responsiveness to three bronchial provocation tests in patients with asthma. *Chest*. 2003;124(6):2171–2177. doi:10.1378/chest.124.6.2171
29. Kankaanranta H, Harju T, Kilpeläinen M, et al. Diagnosis and pharmacotherapy of stable chronic obstructive pulmonary disease: the finnish guidelines. *Basic Clin Pharmacol Toxicol*. 2015;116(4):291–307. doi:10.1111/bcpt.12366
30. Kainu A, Rouhos A, Sovijärvi A, Lindqvist A, Sarna S, Lundbäck B. COPD in Helsinki, Finland: socioeconomic status based on occupation has an important impact on prevalence. *Scand J Public Health*. 2013;41(6):570–578. doi:10.1177/1403494813484554
31. Cloutier MM, Dixon AE, Krishnan JA, Lemanske RF Jr, Pace W, Schatz M. Managing asthma in adolescents and adults: 2020 asthma guideline update from the national asthma education and prevention program. *JAMA*. 2020;324(22):2301–2317. doi:10.1001/jama.2020.21974

Supplementary material

β2-adrenoceptor agonists in asthma or chronic obstructive pulmonary disease and risk of Parkinson's disease: nested case-control study

Anne Paakinaho, Miia Tiihonen, Heikki Koskela, Marjaana Koponen, Jari Tiihonen, Sirpa Hartikainen, Anna-Maija Tolppanen

Supplementary Table 1. Definition of asthma and COPD.

ICD code or classification number	Data source and time period
Asthma	
ICD-10: J45*, J46*	Finnish Care Register for Health Care 1996-2012
ICD-9: 493*	Finnish Care Register for Health Care 1987-1995
ICD-8: 49300, 49302, 49308, 49309	Finnish Care Register for Health Care 1972-1986
Special reimbursement for medication: classification number 203 or 210 along with one of the abovementioned ICD-9 or ICD-10 codes	Special Reimbursement Register 1972-2012
COPD	
ICD-10: J43*, J44*	Finnish Care Register for Health Care 1996-2012
ICD-9: 4912A, 4912B, 492, 4920A, 4928A, 4928X	Finnish Care Register for Health Care 1987-1995
ICD-8: 49104, 49201, 49202, 49209	Finnish Care Register for Health Care 1972-1986
Special reimbursement for medication: classification number 203 or 210 along with one of the abovementioned ICD-9 or ICD-10 codes	Special Reimbursement Register 1972-2012
Asthma and COPD	
Abovementioned definitions were met for both asthma and COPD	

Abbreviations: COPD=chronic obstructive pulmonary disease; ICD=International Classification of Diseases

*Indicates that all diagnosis codes that begin with these characters are included

Supplementary Table 2. Anatomical Therapeutic Chemical (ATC) codes to define exposure to inhaled β2AR agonists, corticosteroids, and anticholinergics. DDDs are according to single active ingredient for inhaled β2AR agonists. For combination products, see World Health Organizations List of DDDs combined products.[1]

Inhaled β2AR agonists	**ATC codes**	**DDD of single active ingredient**
Short-acting β2AR agonists		
salbutamol	R03AC02, R03AL02	0.8 mg (inhaled), 10 mg (nebulized)
terbutaline	R03AC03	2 mg (inhaled), 20 mg (nebulized)
fenoterol	R03AC04, R03AL01	0.6 mg (inhaled), 4 mg (nebulized)
Long-acting β2AR agonists		
salmeterol	R03AC12, R03AK06	0.1 mg (inhaled)
formoterol	R03AC13, R03AK07, R03AK08, R03AK11, R03AL05	24 µg (inhaled)
indacaterol	R03AC18, R03AL04	0.15 mg (inhaled)
olodaterol	R03AC19	5 µg (inhaled)
vilanterol (only in combinations)	R03AK10, R03AL03	
Inhaled corticosteroids	**ATC codes**	**-**
beclometasone	R03BA01, R03AK08	
budesonide	R03BA02, R03AK07	
fluticasone propionate	R03BA05, R03AK06, R03AK11	
mometasone	R03BA07	
ciclesonide	R03BA08	
fluticasone furoate	R03AK10	
Inhaled anticholinergics	**ATC codes**	**-**
Short-acting muscarinic antagonist		
ipratropium bromide	R03BB01, R03AL01, R03AL02	
oxitropium bromide	R03BB02	
Long-acting muscarinic antagonist		
tiotropium bromide	R03BB04	
aclinidium bromide	R03BB05, R03AL05	
glycopyrronium bromide	R03BB06, R03AL04	
umeclidinium bromide	R03BB07, R03AL03	

Abbreviations: β2AR=β2-adrenoceptor; DDD=defined daily dose

Reference:

1. WHOCC - List of DDDs combined products. Accessed May 17, 2022. https://www.whocc.no/ddd/list_of_ddds_combined_products/

Supplementary Table 3. Definitions of covariates.

ATC code, ICD code or classification number	Data source
Cancer history	
ICD-10 code from IARC CRG Tools: C00-C97	Cancer registry since 1972
Cardiovascular diseases	
Special reimbursement for medication: classification number 201, 205, 206, 207, 213, 280	Special Reimbursement Register since 1972
Diabetes	
ICD-10: E10-E14	Finnish Care Register for Health Care since 1996
ICD-9: 250	Finnish Care Register for Health Care 1987-1995
Special reimbursement for medication: classification number 103	Special Reimbursement Register since 1972
Traumatic brain injury	
ICD-10: S06*	Finnish Care Register for Health Care since 1996
ICD-9: 850-854	Finnish Care Register for Health Care 1987-1995
Stroke	
ICD-10: I60-I64	Finnish Care Register for Health Care since 1996
ICD-9: 430-432	Finnish Care Register for Health Care 1987-1995
Substance abuse	
ICD-10: F10-F19, G31.2, G62.1, G72.1, I42.6, K29.2, K70, K86.0, R78.0, T51.0, T51.1, T51.9, X45 and Reason for admission: codes 33, 71-75	Finnish Care Register for Health Care since 1996
ICD-9: 291, 292, 303-305, 980, 3575, 3594, 4255, 5353, 7903, 5710A, 5711A, 5712A, 5713A, 5713X, 5771C, 5771D and Reason for admission: codes 33, 71-75	Finnish Care Register for Health Care 1987-1995
ATC code: N07BB, N07BC	Prescription Register since 1995

Abbreviations: ATC= Anatomical Therapeutic Chemical; IARC CRG= International Agency for Research on Cancer Collaborative Research Group; ICD=International Classification of Diseases
*Indicates that all diagnosis codes that begin with these characters are included

Supplementary Table 4. Exposure to inhaled corticosteroids and anticholinergics before 3-year lag among Parkinson's disease (PD) cases and controls with asthma/chronic obstructive pulmonary disease.

	Controls N=8630 n (%)	PD cases N=1406 n (%)	P
Inhaled corticosteroids	7218 (83.6)	1176 (83.6)	0.998
beclometasone	3264 (37.8)	511 (36.3)	0.29
budesonide	3665 (42.5)	598 (42.5)	0.96
fluticasone propionate	3490 (40.4)	557 (39.6)	0.56
ciclesonide	37 (0.4)	6 (0.4)	0.99
mometasone	2 (0.02)	-	
fluticasone furoate	-	-	
Inhaled anticholinergics	2141 (24.8)	359 (25.5)	0.56
Short-acting muscarinic antagonist	1842 (21.3)	308 (21.9)	0.63
ipratropium bromide	1740 (20.2)	299 (21.3)	0.34
oxitropium bromide	144 (1.7)	16 (1.1)	0.14
Long-acting muscarinic antagonist	647 (7.5)	110 (7.8)	0.67
tiotropium bromide	647 (7.5)	110 (7.8)	0.67
aclinidium bromide	-	-	
glycopyrronium bromide	-	-	
umeclidinium bromide	-	-	

Supplementary Table 5. Dose-response associations between use of inhaled β2AR agonists and PD, the lowest tertile as reference. β2AR agonist exposure has occurred before 3-year lag period and analyses were restricted to users only.

Short-acting β2AR agonists	**Controls N=6199 n (%)**	**PD cases N=1177 n (%)**	**OR (95% CI)**	**Adjusted[a] OR (95% CI)**
Cumulative DDD				
7-118 DDD	2071 (33.4)	385 (32.7)	Reference	Reference
120-425 DDD	2058 (33.2)	414 (35.2)	1.08 (0.92-1.26)	1.07 (0.92-1.26)
430-14016 DDD	2070 (33.4)	378 (32.1)	0.93 (0.78-1.09)	0.92 (0.78-1.09)
Annual exposure				
7-41 DDD/year	2032 (32.6)	385 (32.7)	Reference	Reference
42-88 DDD/year	2110 (34.0)	415 (35.3)	1.03 (0.88-1.21)	1.02 (0.88-1.20)
89-1533 DDD/year	2066 (33.3)	377 (32.0)	0.87 (0.74-1.03)	0.86 (0.73-1.01)
Long-acting β2AR agonists	**Controls N=2240 n (%)**	**PD cases N=649 n (%)**	**OR (95% CI)**	**Adjusted[a] OR (95% CI)**
Cumulative DDD				
15-420 DDD	735 (32.8)	230 (35.4)	Reference	Reference
435-1620 DDD	747 (33.4)	225 (34.7)	1.01 (0.82-1.26)	1.02 (0.82-1.27)
1635-11010 DDD	758 (33.8)	194 (29.9)	0.89 (0.70-1.13)	0.89 (0.70-1.14)
Annual exposure				
15-140 DDD/year	734 (32.8)	232 (35.8)	Reference	Reference
141-279 DDD/year	730 (32.6)	226 (34.8)	1.02 (0.82-1.26)	1.02 (0.82-1.27)
280-1032 DDD/year	776 (34.6)	191 (29.4)	0.81 (0.65-1.02)	0.82 (0.65-1.02)
Any β2AR agonist	**Controls N=6632 n (%)**	**PD cases N=1219 n (%)**	**OR (95% CI)**	**Adjusted[a] OR (95% CI)**
Cumulative DDD				
6-232 DDD	2184 (32.9)	429 (35.2)	Reference	Reference
233-1272 DDD	2213 (33.4)	405 (33.2)	0.94 (0.81-1.09)	0.93 (0.80-1.09)
1275-15246 DDD	2235 (33.7)	385 (31.6)	0.85 (0.73-1.00)	0.85 (0.72-1.00)
Annual exposure				
6-64 DDD/year	2196 (33.1)	419 (34.4)	Reference	Reference
65-205 DDD/year	2204 (33.2)	412 (33.8)	0.97 (0.84-1.13)	0.97 (0.83-1.13)
206-1691 DDD/year	2232 (33.7)	388 (31.8)	0.87 (0.74-1.02)	0.87 (0.74-1.02)

[a]Cancer history, cardiovascular diseases, diabetes, socioeconomic position, stroke, substance abuse and traumatic brain injury

Abbreviations: β2AR=β2-adrenoceptor; CI=confidence interval; OR=Odds ratio; PD=Parkinson's disease

Supplementary Table 6. Dose-response associations between use of inhaled β2AR agonists and PD, the lowest quartile as reference. Odds ratios for unadjusted model, model adjusted with standard covariates and model further adjusted with inhaled corticosteroids and anticholinergics.

Short-acting β2AR agonists	**OR (95% CI)**	**Adjusted[a] OR (95% CI)**	**Adjusted[b] OR (95% CI)**
Cumulative DDD			
7-75 DDD	Reference	Reference	Reference
78-223 DDD	1.07 (0.90-1.28)	1.06 (0.89-1.27)	1.05 (0.88-1.26)
225-633 DDD	0.99 (0.82-1.18)	0.98 (0.82-1.17)	0.96 (0.80-1.15)
635-14016 DDD	0.84 (0.70-1.02)	0.84 (0.69-1.02)	0.82 (0.67-1.00)
Annual exposure			
7-33 DDD/year	Reference	Reference	Reference
34-57 DDD/year	1.01 (0.85-1.21)	1.01 (0.85-1.20)	1.00 (0.84-1.20)
58-113 DDD/year	0.94 (0.79-1.13)	0.93 (0.78-1.12)	0.92 (0.77-1.11)
114-1533 DDD/year	0.92 (0.76-1.11)	0.91 (0.75-1.10)	0.90 (0.74-1.09)
Long-acting β2AR agonists	**OR (95% CI)**	**Adjusted[a] OR (95% CI)**	**Adjusted[b] OR (95% CI)**
Cumulative DDD			
15-240 DDD	Reference	Reference	Reference
255-900 DDD	0.93 (0.73-1.19)	0.94 (0.73-1.21)	0.94 (0.73-1.20)
915-2100 DDD	0.88 (0.68-1.14)	0.89 (0.69-1.16)	0.89 (0.69-1.15)
2115-11010 DDD	0.88 (0.67-1.15)	0.88 (0.67-1.16)	0.88 (0.66-1.15)
Annual exposure			
15-105 DDD/year	Reference	Reference	Reference
107-210 DDD/year	0.90 (0.70-1.16)	0.91 (0.71-1.17)	0.91 (0.71-1.17)
212-310 DDD/year	0.93 (0.72-1.19)	0.94 (0.73-1.21)	0.93 (0.73-1.20)
311-1032 DDD/year	0.74 (0.57-0.97)	0.75 (0.58-0.97)	0.74 (0.57-0.97)
Any β2AR agonist	**OR (95% CI)**	**Adjusted[a] OR (95% CI)**	**Adjusted[b] OR (95% CI)**
Cumulative DDD			
6-148 DDD	Reference	Reference	Reference
150-555 DDD	1.12 (0.94-1.33)	1.11 (0.93-1.32)	1.08 (0.91-1.30)
560-1848 DDD	1.06 (0.89-1.27)	1.06 (0.89-1.27)	1.03 (0.86-1.24)
1850-15246 DDD	0.85 (0.70-1.03)	0.85 (0.70-1.03)	0.82 (0.67-1.01)
Annual exposure			
6-49 DDD/year	Reference	Reference	Reference
50-120 DDD/year	1.17 (0.98-1.39)	1.16 (0.97-1.38)	1.15 (0.96-1.37)
121-259 DDD/year	1.11 (0.92-1.33)	1.11 (0.92-1.33)	1.09 (0.90-1.31)
260-1691 DDD/year	0.92 (0.76-1.11)	0.92 (0.76-1.11)	0.90 (0.74-1.09)

[a]Cancer history, cardiovascular diseases, diabetes, socioeconomic position, stroke, substance abuse and traumatic brain injury

[b]In addition to [a]: inhaled corticosteroids and anticholinergics.

Abbreviations: β2AR=β2-adrenoceptor; CI=confidence interval; OR=Odds ratio; PD=Parkinson's disease

ANNE PAAKINAHO

The causes of Parkinson's disease are often unknown, and little is known about modifiable risk factors. This nationwide register-based study investigated whether disease-modifying antirheumatic drugs and inhaled β2-adrenoceptor agonists are associated with the risk of Parkinson's disease in indication-restricted studies. Furthermore, the incidence of muscle relaxant use was investigated as proxy for musculoskeletal symptoms while revealing an appropriate exposure assessment period for risk factor studies to control for reverse causality.

UNIVERSITY OF
EASTERN FINLAND

uef.fi

PUBLICATIONS OF
THE UNIVERSITY OF EASTERN FINLAND
Dissertations in Health Sciences

ISBN 978-952-61-5094-9
ISSN 1798-5706