



HAL
open science

Ten years preceding a diagnosis of neurodegenerative disease in Europe and Australia: medication use, health conditions, and biomarkers associated with Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis

Dang Wei, Anna Freydenzon, Octave Guinebretiere, Karim Zaidi, Fen Yang, Weimin Ye, Niklas Hammar, Karin Modig, Naomi R Wray, Maria Feychting, et al.

► **To cite this version:**

Dang Wei, Anna Freydenzon, Octave Guinebretiere, Karim Zaidi, Fen Yang, et al.. Ten years preceding a diagnosis of neurodegenerative disease in Europe and Australia: medication use, health conditions, and biomarkers associated with Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis. *EBioMedicine*, 2025, 113, pp.105585. <10.1016/j.ebiom.2025.105585>. <hal-05028859>

HAL Id: hal-05028859

<https://hal.science/hal-05028859v1>

Submitted on 10 Apr 2025

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire HAL, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons CC BY 4.0 - Attribution - International License

**Ten years preceding a diagnosis of neurodegenerative disease in Europe and Australia:
Medication use, health conditions, and biomarkers associated with Alzheimer's disease,
Parkinson's disease, and amyotrophic lateral sclerosis**

Dang Wei^{1,*}, Anna Freydenzon^{2,*}, Octave Guinebretiere^{3,*}, Karim Zaidi³, Fen Yang¹, Weimin Ye⁴, Niklas Hammar¹, Karin Modig¹, Naomi R. Wray^{2,5}, Maria Feychting¹, Nadine Hamieh³, Bruno Ventelou⁶, Beranger Lekens⁷, Laurene Gantzer⁷, Stanley Durrleman^{3,+}, Allan McRae^{2,+}, Baptiste Couvy-Duchesne^{2,3,+}, Fang Fang^{1,+}, Thomas Nedelec^{3,+}, The LeMeReND consortium.

1. Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden
2. Institute for Molecular Biosciences, The University of Queensland, Brisbane, Australia
3. Sorbonne University, Paris Brain Institute – ICM, CNRS, Inria, Inserm, AP-HP, Hôpital de la Pitié Salpêtrière, Paris, France
4. Department of Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden
5. Department of Psychiatry, University of Oxford, Oxford, the UK
6. Aix-Marseille University, CNRS, IRD, AMSE, Marseille, France
7. Cegedim R&D, Boulogne-Billancourt, France

*These authors contributed equally to this work.

+These authors contributed equally to this work.

Correspondence to: Dang Wei, Institute of Environmental Medicine, Karolinska Institutet, Nobels väg 13, 17177 Stockholm, Sweden; dang.wei@ki.se; +46 738761749

Word count of abstract: 290

Word count of the main text: 4465

Summary

Background

Many studies have investigated early predictors for Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS). However, evidence is sparse regarding specific and common predictors for these diseases. We aimed to identify medication use, health conditions, and blood biomarkers that might be associated with the risk of AD, PD, and ALS ten years later.

Methods

We conducted population-based nested case-control studies of AD, PD, and ALS using electronic medical records in Europe (France, the UK, and Sweden) and Australia. We retrieved data on medication use, diagnosed health conditions, and measured blood biomarkers from electronic medical records or biomedical cohorts. Conditional logistic regression models and meta-analysis were applied to assess the associations between these prodromal factors and the risk of receiving a diagnosis of AD, PD, or ALS.

Findings

We included a total of 149,642 AD cases (mean age: 79.1-81.2 years), 252,696 PD cases (73.2-75.9 years), and 27,533 ALS cases (64.4-69.6 years). The prescription of psychoanaleptics and nasal preparations was consistently associated with an increased risk of AD, PD, and ALS 5-10 years later. Constipation and use of related medications were associated with an increased risk of AD and PD, while diabetes and use of antidiabetics were associated with a reduced risk of ALS. A higher level of triglycerides was associated with a lower risk of AD, whereas a higher level of Apolipoprotein B was associated with a lower risk of PD, 5-10 years later.

Interpretation

Psychoanaleptics and nasal preparations may serve as common predictors for diagnosis of AD, PD, and ALS 5-10 years later. Conversely, the increased prevalence of constipation is specific to AD and PD, while the decreased prevalence of diabetes and use of antidiabetics are specific to ALS.

Funding

EU Joint Programme – Neurodegenerative Disease Research.

Keywords: neurodegenerative disease; Alzheimer's disease; Parkinson's disease; amyotrophic lateral sclerosis; medications; health conditions; biomarkers.

Research in context

Evidence before this study

We searched PubMed from inception until May 30, 2024 for English original articles using the following search strategy: ("dementia" [Title/Abstract] OR "alzheimer" [Title/Abstract] OR "parkinson" [Title/Abstract] OR "amyotrophic lateral sclerosis" [Title/Abstract] OR "ALS" [Title/Abstract]) AND ("prodromal" [Title/Abstract] OR "prediagnostic" [Title/Abstract] OR "pre-diagnostic" [Title/Abstract]). We screened for studies with a focus on medications, health conditions, and blood biomarkers during the prodromal stage (up to 20 years) of the three neurodegenerative diseases (i.e., Alzheimer's disease [AD] and other dementias, Parkinson's disease [PD], and amyotrophic lateral sclerosis [ALS]) and found 18 studies (6 in AD and other dementias, 9 in PD, 2 in ALS, and 1 in both AD and PD). Most of the studies focused on a single or group of prodromal factors, but there are six data-driven studies that evaluated medications and health conditions before the diagnosis of AD and other dementias, and PD. Briefly, these studies identified several common factors that are associated with the risk of AD and other dementias, and PD, a few years later (e.g., 0-2 or 2-10 years), including depression, anxiety, constipation, sleep issues, memory loss, fatigue, and low body weight. In contrast, some prodromal factors were only observed for specific diseases, e.g., stress-related disorders, hypertension, arthritis, vision impairment, coronary heart disease, stroke, diabetes, loneliness, and benzodiazepines use, etc., for AD and other dementias; fracture, hypotension, and use of antibiotics, psychoanaleptics, medicines for constipation, urologicals, etc., for PD; and a high level of plasma neurofilament light chain for ALS. Previous studies utilized various data sources (e.g., established cohorts, national registries) and focused on different timeframes prior to diagnosis, leading to a challenge in directly comparing results across studies. Further, none of the studies has attempted to

identify common prodromal factors, including medications, health conditions, and blood biomarkers, across the three neurodegenerative diseases.

Added value of this study

The study leverages data from Australia, France, the UK, and Sweden with the aim to identify medications, health conditions, and blood biomarkers associated with the risk for AD, PD, and ALS during the prodromal stage (2-5 and 5-10 years prior to diagnosis). Meta-analyses were conducted for 49 medications and 73 health conditions in AD, 45 medications and 134 health conditions in PD, and 43 medications and 131 health conditions in ALS. Psychoanaleptics and nasal preparations were found to be consistently associated with an increased risk of AD, PD, and ALS 5-10 years later. Several indications for psychoanaleptics, e.g., depression, anxiety, sleep disorders, etc., were also associated with the risk of AD and PD 5-10 years later. Similar results were exhibited for constipation and use of related medications in relation to AD and PD. Finally, diabetes and use of antidiabetics were found to be consistently associated with a lower future risk of ALS.

Implications of all available evidence

Together with the existing knowledgebase, this work adds on important evidence for identifying individuals at high risk of developing neurodegenerative diseases using information on medication use, diagnosed health conditions, and blood biomarkers. It also provides potential targets for impeding the progression or postponing the onset of these neurodegenerative diseases.

Introduction

Neurodegenerative diseases (NDDs) pose a significant public health challenge due to their rising prevalence among aging populations and substantial healthcare expenditure.(1-3) Alzheimer's disease (AD) and other dementias, affecting 52 million people in 2019,(2) are estimated to impact 150 million in 2050, worldwide.(4) Parkinson's disease (PD), the second most common NDD, affected 6.1 million people in 2016, representing a 145% increase since 1990.(3) Motor neuron disease (MND), with amyotrophic lateral sclerosis (ALS) as the major type, is also on the rise, affecting about 160,000 individuals in 1990 and 269,000 in 2019.(5)

Several factors, including depression, anxiety, constipation, sleep issues, memory loss, fatigue, and low body weight, have been found to be associated with an increased risk of AD and other dementias and PD up to 10 years later in previous studies.(6-9) However, there is a challenge to compare findings across studies as they used various data sources and focused on different timeframes prior to NDDs diagnosis and none has attempted to evaluate factors that are commonly associated with several NDDs. It remains unclear whether any prescribed medications and blood biomarkers could be commonly predictive of future NDDs and whether the results are consistent across populations with different healthcare systems.

To this end, we set up an international consortium utilizing electronic medical records and biomedical cohort data from Australia, France, the UK, and Sweden, covering a common timeframe up to 10 years before the diagnosis of NDDs. We systematically evaluated a series of prescribed medications, clinically diagnosed health conditions, and blood biomarkers that preceded the diagnosis of AD, PD, and ALS. We sought to identify a comprehensive list of potential predictors for future NDDs, which are either specific or generic to different NDDs and applicable to various populations.

Methods

Data sources

Australia

The Australian Institute of Health and Wellness is an independent statutory agency that collects, analyses, and disseminates Australian health and welfare data, including performing linkage across national data collections, particularly the National Death Index (NDI) and Pharmaceutical Benefits Scheme (PBS). The NDI consists of all records of death in Australia since 1980, with information on the date and the main and secondary causes of death. The PBS data collection, started in 1984, meticulously records prescriptions eligible for benefits, encompassing information on drug categorization, costs, the prescriber, and the dispensing pharmacy. The data used in this study were obtained from the Australian Institute of Health and Wellness and incurred an extraction fee.

France: SNDS

The French National Health Data System (SNDS) is a comprehensive and extensive repository of healthcare information established in 2009 with the aim to catalog all reimbursements from public health insurance for all residents in France. The repository incorporates data from two primary sources: the national hospital discharge database for inpatient care and the national health insurance claims information system for outpatient care, covering approximately 99% of the population of France. SNDS contains detailed information on all reimbursed prescriptions in both inpatient and outpatient services. SNDS also includes information on clinical diagnoses from hospitalization records and long-term disease scheme, which lists and reimburses conditions specifically to alleviate the financial hardship. To access and process data from the SNDS, permanent access to the CNAM data portal was

granted via the INRIA affiliation of the ARAMIS team, in application of the provisions of Articles R. 1461-11 to R. 1461-17 of the French Public Health Code and the French data protection authority decision CNIL-2016-316.

France and the UK: THIN

The Health Improvement Network (THIN) database that contains primary care data from France and the UK. The THIN database contains information on prescribed medications and clinical diagnoses from 2,500 general practitioners in France and 532 general practitioners in the UK, including 8 million patients in total. The French data are representative of the French general population in terms of age, sex, and residence. The UK data, accounting for around 6% of the UK population, accurately reflect the demographics and types of consultation found within the entire UK population. The data are available from the Cegedim company upon request for researchers who meet the criteria for access to confidential data.

Sweden

The Swedish Total Population Register contains demographic information of residents who lived and were registered in Sweden at any time since 1960s. The National Patient Register had been collecting information on inpatient care since 1964 (nationwide since 1987) and on outpatient care since 2001, enabling us to identify cases of NDDs and health conditions prior to diagnosis of NDDs. The National Prescribed Drug Register, initiated in 2005, collects all prescriptions and dispensations in Sweden, allowing use to identify medication use before the diagnosis of NDDs.

The Swedish Apolipoprotein-related MOrtality RiSk (AMORIS) cohort is a population-based study including 812,073 individuals undergoing health examinations during 1985-1996 who mainly resided in the Stockholm region. The health examinations included the collection of

blood or urine samples from either a routine occupational health check-up or through outpatient care. Participants have been followed through the linkage to several national health data and population registries. These registries are kept by Swedish authorities (the National Board of Health and Welfare and Statistics Sweden) for administrative purposes and can be used for research purposes after permission from the Swedish Ethical Review Authority and a legal assessment by the registry holder.

Study design

We conducted several nested case-control studies to assess prescribed medications, health conditions, and blood biomarkers preceding AD, PD, and ALS. We identified these NDDs in each country simultaneously (detailed in Table S1 and in Supplementary Methods). The date of the first diagnosis of AD, PD, and ALS was defined as the index date respectively. We randomly selected one control (in the analysis of AD in France and the UK; and the analysis of PD in France) or ten controls per case of NDD, who were free of any NDD at the index date and individually matched to the NDD case by sex and year of birth, detailed in Supplementary Methods. Information on sex for all countries was sourced from administrative databases. Our primary analysis focused on prescribed medications associated with these NDDs using data from all four countries (AD: 79,013 cases and 433,082 controls; PD: 213,784 cases and 377,665 controls; ALS: 23,748 cases and 237,480 controls). In a secondary analysis, we evaluated whether there were clinically diagnosed health conditions associated with these NDDs using data from France, the UK, and Sweden (AD: 149,553 cases and 1,138,483 controls; PD: 252,696 cases and 766,785 controls; ALS: 27,533 cases and 275,330 controls). Moreover, we investigated if biomarkers commonly measured in clinical chemistry were associated with NDDs in Sweden (AD: 22,294 cases and 222,940 controls; PD: 9000 cases and 90,000 controls; ALS: 1215 cases and 12,150 controls; Figure 1).

We identified all prescribed medications and clinically diagnosed health conditions before the index date using Anatomical Therapeutic Chemical (ATC) and International Classification of Diseases (ICD) codes respectively. Health conditions were grouped by clinical or biological similarities (Table S2-6). As the first three digits of ATC codes were commonly available in our databases, we studied all families of prescribed medications identified by the first three digits. Eventually, there were 68 medications available for the analysis of ALS in Australia, 86 for AD, 67 for PD, and 65 for ALS in France, 84 for AD in the UK, as well as 55 for AD, PD, and ALS in Sweden. To limit the number of statistical tests, we selected health conditions that were recorded in >0.1% of medical visits per 1000 person-years among cases of each NDDs. Finally, we selected 98 health conditions for AD, 237 for PD, and 206 for ALS in France, 98 for AD in the UK, as well as 153 for AD, 160 for PD, and 175 for ALS in Sweden.

Ethics

Written informed consent from study participants was not needed as we only utilized administrative data for analysis in this study. Further, no steps were taken for patient and public involvement in the research study. As permanent users of the SNDS, we declared the analyses in France and the UK to the INRIA's SNDS registry and were exempted from Institutional Review Board approval. The analyses in Australia and Sweden have been approved by the Australian Institute of Health and Wellness Ethics Committee (EO2019/1/481) and the Swedish Ethical Review Authority (30943/2016; 2018/2401-31), respectively.

Statistics

We calculated incidence rate ratios (IRR) and 95% confidence intervals (CI) for the associations of prescribed medications and health conditions with AD, PD, and ALS

diagnosed years later in each country, using conditional logistic regression. As we applied nested case-control study design in which all study individuals are followed from the year of data availability and the lengths of follow-up for case and control(s) in the matched risk set are identical, IRR can be estimated from conditional logistic regression. We disregarded the first two years before the index date to eliminate or diminish reverse causality, as the average diagnostic delay ranges from 1 to 7.5 years for NDDs.(10-12) To further eliminate reverse causality caused by diagnostic delay, we analysed prescribed medications and health conditions for the periods of 2-5 and 5-10 years before the index date separately. We defined individuals as exposed when the studied prescribed medications and health conditions were identified at least once during the two periods separately. As we were mostly interested in 5-10 years before diagnosis of NDDs, we also performed the analysis for prescribed medications 5-10 years prior to the index date among men and women separately. Given that NDDs often have prodromal phases longer than a decade, we also analysed health conditions occurring >10 years before the index date in Sweden, where extensive data on health conditions were available for periods exceeding 10 years prior to diagnosis.

As participants of the AMORIS cohort were relatively young at the baseline health examination (mean: 43 years), we performed the analyses of blood biomarkers for the periods of 5-10 and >10 years before the index date separately. To assure sufficient statistical power, we also re-ran the analysis of blood biomarkers with period of ≥ 2 years before the index date. Blood biomarkers were categorized according to sex-specific clinical cutoffs and the lower levels of the biomarkers were defined as the reference group. We adjusted for sex, country of birth, calendar year of blood sampling, calendar year of the index date, and age at the index date in the analysis of blood biomarkers. The covariates were considered as potential confounders if they were (1) causes of blood biomarkers or NDD or both, (2) proxies for unmeasured common causes of blood biomarkers and NDD, and (3) not an instrumental

variable. We meta-analysed the country-specific results of prescribed medications and health conditions using the DerSimonian and Laird method of random effect models and defined statistical significance as P -value $<0.05/\text{number of tests}$, corresponding to Bonferroni correction for multiple comparison. Confidence intervals were calculated according to the alpha level of $0.05/\text{number of tests}$ in two-tailed tests. To account for the potential bias in meta-analysis with few studies, we re-run the meta-analysis for medications 5-10 years before AD, PD, and ALS using the Hartung-Knapp-Sidik-Jonkman method of random effect models.(13, 14) The meta-analyses were only performed for the medications and health conditions that were analysed in all specific countries. There were 49 families of medications available for the meta-analysis of AD from France, the UK, and Sweden, 45 for PD from France and Sweden, and 43 for ALS from Australia, France, and Sweden. We meta-analyzed a total of 73 health conditions from France, the UK, and Sweden for AD, 134 from France and Sweden for PD, as well as 131 from France and Sweden for ALS. We ultimately meta-analysed 49 families of medications for AD across France, the UK, and Sweden; 45 medications for PD across France and Sweden; and 43 medications for ALS across Australia, France, and Sweden. Additionally, we analysed 73 health conditions associated with AD across France, the UK, and Sweden; 134 associated with PD across France and Sweden; and 131 associated with ALS across France and Sweden.

Role of Funders

The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the paper.

Results

We included a total of 149,553 cases and 1,138,482 controls for the analysis of AD, 252,696 cases and 766,785 controls for PD, as well as 27,533 cases and 275,330 controls for ALS (Table 1). The mean ages at the diagnosis of AD and PD were similar across countries (79-81 and 73-76 years, respectively), while patients with ALS in Australia were diagnosed at a relatively younger age than in France and Sweden (64 vs. 68 vs. 70 years). Sex differences in the incidence of NDDs were consistent across countries, with a female predominance in AD but a male predominance in PD and ALS.

Prescribed medications before the diagnosis of AD, PD, and ALS

We observed from meta-analyses that psychoanaleptics and nasal preparations were more frequently prescribed 5-10 years before the diagnosis of AD [IRR (95%CI): 1.53 (1.16-2.02) and 1.13 (1.03-1.25) respectively], PD [1.38 (1.32-1.45) and 1.10 (1.03-1.18)], and ALS [1.11 (1.04-1.19) and 1.12 (1.05-1.20)], compared with controls ($P < 0.05$ from Wald test; Figure 2; Table S7-10). We also found that individuals with AD and PD, respectively, compared with controls, had more prescribed use of medicines for constipation [1.22 (1.09-1.37) and 1.31 (1.27-1.36)], sex hormones and modulations of the genital system [1.20 (1.03-1.41) and 1.15 (1.10-1.21)], vasoprotectives [1.14 (1.02-1.29) and 1.09 (1.01-1.16)], and muscle relaxants [1.14 (1.02-1.27) and 1.09 (1.05-1.13)] 5-10 years before diagnosis. In contrast, medications for acid-related disorders were more frequently prescribed 5-10 years before the diagnosis of PD and ALS [1.16 (1.10-1.21) and 1.10 (1.02-1.18) respectively]. Compared to controls, patients with AD exhibited a reduced likelihood of being prescribed anti-obesity preparations during 5-10 years before diagnosis [0.78 (0.62-0.99)]. Patients with PD had a higher risk of being prescribed medications for functional gastrointestinal disorders [1.20 (1.06-1.36)], antidiarrheals [1.09 (1.05-1.13)], beta blocking agents [1.05 (1.01-1.09)], gynecological anti-infectives and antiseptics [1.10 (1.03-1.18)], urologicals [1.33 (1.17-1.51)], antimycotics for

system use [1.09 (1.02-1.17)], vaccines [1.11 (1.07-1.15)], drugs for treatment of bone diseases [1.11 (1.01-1.22)], antiepileptics [1.44 (1.19-1.74)], psycholeptics [1.26 (1.22-1.30)], cough and cold preparations [1.07 (1.01-1.12)], antihistamines for systemic use [1.10 (1.04-1.16)], and ophthalmologicals [1.14 (1.10-1.17)] during 5-10 years before diagnosis, compared to controls. In contrast, Patients with ALS had a lower risk of being prescribed antidiabetics [0.71 (0.56-0.89)] and antihypertensives [0.82 (0.69-0.97)], but a higher risk of being prescribed stomatological preparations [1.10 (1.03-1.19)] and corticosteroids for system use [1.10 (1.03-1.18)], than controls. The results from the Hartung-Knapp-Sidik-Jonkman method of random effect models were largely similar (Table S8-10). Furthermore, similar associations were observed for the period of 2-5 years before diagnosis (Table S11-13). The incidence rate of prescribed medications for constipation, urologicals, antiepileptics, psycholeptics, and psychoanaleptics increased over the 10 years prior to diagnosis in both cases and controls of AD, PD, and ALS. However, the increase was higher in cases compared to controls (Figure S6). The associations observed in men and women respectively were largely similar to those in the entire study population (Table S14-19).

Health conditions before the diagnosis of AD, PD, and ALS

In line with the results on psychoanaleptics, the meta-analysis showed that, compared to controls, patients with AD had a higher prevalence of depression [1.39 (1.20-1.61)], anxiety [1.31 (1.15-1.49)], and sleep disorder [1.16 (1.01-1.34)], whereas patients with PD had a higher prevalence of depression [1.70 (1.41-2.05)], schizophrenia [2.00 (1.66-2.41)], and bipolar disorder [2.21 (1.82-2.68)] during 5-10 years before diagnosis ($P < 0.05$ from Wald test; Figure 3; Table S20-22). Both patients with AD and PD had an elevated prevalence of constipation during 5-10 years prior to diagnosis [1.43 (1.17-1.73) and 1.44 (1.04-1.99) respectively]. Diabetes was observed to be associated with a lower risk of ALS [0.75 (0.62-

0.92)], but such an association was not found for AD [0.96 (0.63-1.47)] or PD [1.04 (0.84-1.29)] (Table S23). In contrast, acute myocardial infarction [0.86 (0.77-0.96)] and atherosclerosis [0.79 (0.64-0.98)] were less prevalent among patients with PD, compared to controls, during 5-10 years before diagnosis (Table S22). These associations were mostly observed for the period of 2-5 years and >10 years before diagnosis (Table S24-29).

Blood biomarkers before the diagnosis of AD, PD, and ALS

A higher level of triglycerides was associated with a lower risk of AD 5-10 years later [0.69 (0.50-0.95)] (Table 2; Table S30-32). Similar association was found for Apolipoprotein B (ApoB) and PD [0.60 (0.37-0.97)]. Compared with controls, patients with AD had higher levels of ApoB [1.13 (1.01-1.25)], ApoB/apolipoprotein A (ApoA) ratio [1.16 (1.04-1.30)], low-density lipoprotein (LDL) [1.17 (1.02-1.35)], and LDL/high-density lipoprotein (HDL) ratio [1.13 (1.03-1.23)] measured >10 years earlier. In contrast, patients with PD had lower levels of ApoB [0.85 (0.72-1.00)], triglycerides [0.79 (0.67-0.92)], and leukocyte [0.69 (0.51-0.94)] than controls. We did not observe clear associations for ALS.

Discussion

Our large-scale multinational population-based study from Australia, France, the UK, and Sweden showed that the prescription of psychoanaleptics and nasal preparations was associated with an increased risk of AD, PD, and ALS 5-10 years later. Findings from the meta-analyses also suggested that potential indications for the prescription of psychoanaleptics, e.g., depression, anxiety, sleep disorder, schizophrenia, and bipolar disorder, were associated with an elevated risk of AD and PD 5-10 years later. Overall, we identified a total of 23 groups of medications that were associated with an increased risk of at least one NDD 5-10 years following the prescription. We also found that individuals with higher-than-

normal levels of ApoB, ApoB/ApoA ratio, LDL, and LDL/HDL ratio had an increased risk of AD >10 years later, whereas those with higher-than-normal levels of ApoB, triglycerides, and leukocyte had a reduced risk of PD >10 years later.

The present study comprehensively compared medical indices for NDDs, including prescribed medications, clinically diagnosed health conditions, and blood biomarkers, using population-based data from Australia, France, the UK, and Sweden. Running analyses on health registries from multiple countries mitigate biases inherent in single-country studies, e.g., specific population demographics or healthcare system. These databases typically encompass a significantly larger and more diverse patient population compared to traditional cohorts, providing a comprehensive representation of real-world healthcare scenarios.(15) They also offer a unique advantage in their ability to provide extensive temporal coverage compared to traditional research cohorts. The data from all countries consistently show similar average ages at the diagnosis of NDDs, with a consistent pattern where AD is typically diagnosed at the oldest age, followed by PD and then ALS, alongside comparable sex difference in the prevalence of different NDDs. These figures are in line with previous reports.(3, 16) Further, by exhaustively testing all possible associations within large, diverse datasets, we can uncover early indicators and common risk factors that might otherwise be overlooked, ultimately contributing to more effective prevention strategies. The large sample size in this study contributed to the relatively narrow 95% CIs, enhancing the precision of our observed associations.

Our findings align with existing evidence that psychotropic medications and related health conditions are common prodromal factors for NDDs. For example, both the present study and previous research found that psychoanaleptics (predominantly antidepressants) and depression

were associated with an increased risk of subsequent AD and PD a few years later (e.g., 5-10 years).(6-9, 17, 18) The availability of multiple sets of exposures (e.g., medications and health conditions) enabled us to cross-validate and further understand the observed associations. For instance, the findings of the associations of psychoanaleptics and several psychiatric disorders with the risk of subsequent NDDs are mutually supportive. The evidence supporting a relationship between depression and the subsequent risk of ALS is relatively limited.(19, 20) The present study extends current knowledge by revealing that psychoanaleptics prescribed 5-10 years before was associated with a higher risk of ALS. Our findings also showed associations of schizophrenia and bipolar disorders with subsequent AD (in Sweden) and PD, in line with previous studies.(21-24)

Constipation may be an important prodromal symptom of AD and PD. Our analyses consistently showed an elevated risk of AD and PD among individuals with constipation or who were prescribed medications for constipation 5-10 years earlier. These results echo the previously reported associations for AD and other dementias and PD.(6, 8, 9, 18, 25) In contrast, we observed a relationship between prescription of constipation medications and the risk of ALS 5-10 years later in France but not in the meta-analysis. Further studies are required to clarify if constipation is indeed a prodromal symptom for ALS.

Diabetes and antidiabetics are prodromal factors for ALS. Our findings consistently suggest that both the prescription of antidiabetics and the diagnosis of diabetes were associated with a reduced risk of subsequent ALS 5-10 years later. This is in line with previous findings on protective effect of type 2 diabetes identified during the decade before diagnosis on ALS risk.(26) It is well documented that diabetes is associated with the risk of AD and PD,(27, 28) but diabetes was identified at various periods before the diagnosis. The evidence for the

associations of AD and PD in relation to diabetes occurred during the prodromal phase is sparse. Only one study has reported that diabetes diagnosed up to 6 years earlier is associated with a higher risk of AD.(7) We observed associations of diabetes and medications used in diabetes with AD or PD in the Swedish data only but not in the meta-analysis of data from multiple countries (Table S7 and S19-20). As diabetes was ascertained from hospital-based inpatient or outpatient records in the Swedish data, these associations may be limited to diabetes with complications or type 1 diabetes with which patients routinely visit specialists. More work is needed to elucidate the heterogeneity of the associations we observed between countries.

Despite growing evidence showing associations between cardiovascular diseases (e.g., hypertension and ischemic heart disease) and the risk of AD and PD,(29, 30) knowledge on whether cardiovascular diseases and their medications are prodromal factors for AD and PD remains relatively limited.(7, 18, 25) Previous studies reported an association with a higher risk of AD for hypertension diagnosed up to 15 years earlier(7) and of PD for hypotension diagnosed up to 8 years earlier.(25) Our analysis did not confirm these associations but demonstrated that patients with AD had a higher prevalence of varicose veins of lower extremities diagnosed 5-10 years earlier while patients with PD had a lower prevalence of myocardial infarction and atherosclerosis compared to their controls. We found that antihypertensives use was associated with a lower risk of ALS 5-10 years later. Previous smaller studies had, on the other hand, reported mixed results.(26) Furthermore, higher levels of ApoB, ApoB/ApoA ratio, LDL, and LDL/HDL ratio were associated with an increased risk of AD while higher levels ApoB and triglycerides were associated with a reduced risk of PD, >10 years later. Since only the latest measurement of biomarkers during the recruitment period of AMORIS was utilized in our analysis, future investigation is needed to model

trajectories of biomarkers before diagnosis of NDDs and confirm if these biomarkers measured during prodromal stage are indicative of NDDs.

Infection might be a prodromal factor for NDDs. Our prior research, along with findings from other studies, has indicated that both infections and the usage of antibiotics might be associated with increased risks of AD, PD, and ALS.(26, 31, 32) Although the present study did not find a consistent association of either diagnoses of infection or use of anti-infectious medication with the risk of any of the studied NDDs 5-10 years later, the point estimates consistently suggested a positive trend. Additionally, our findings showed that nasal preparations were commonly associated with AD, PD, and ALS. Consistent with previous findings,(33, 34) we observed a trend showing that rhinitis, the most common indication for nasal preparations, was also associated with the three NDDs although the confidence intervals were wide. The wide confidence intervals are likely attributable to the low prevalence of rhinitis in both cases and controls, identified through hospital-based data (inpatient and outpatient care) for PD and ALS in France and Sweden. Mild cases of rhinitis, often managed in primary care, were largely missed in this analysis.

There are several limitations in this study. First, the diversity of data sources has led to a varied prevalence of medications and health conditions across countries, which may have contributed to heterogeneity in the estimates. For instance, anxiety was associated with an increased risk of PD 5-10 years later in France and Sweden. However, the confidence intervals exhibited no overlap between the two countries and the meta-analysis revealed insignificant results. On the other hand, the heterogeneity in data sources helps to ensure that any observed associations are likely robust to varying populations and healthcare systems. Second, the families of medications identified by the first three digits of ATC codes are

relatively broad and can correspond to multiple indicating health conditions, making it challenging to disentangle the links between specific medications and their related diseases and NDDs. While we analysed all recorded medications, for certain prescription there were only a few cases or controls exposed before diagnosis, which may introduce sparse-data bias into the estimations. To avoid misleading results, we did not report estimations for rare medications and excluded them from the meta-analysis. Third, the interpretation of the associations between blood biomarkers and the risk of NDDs should be done with caution as these biomarkers were measured at middle age (mean: 43 years) whereas most NDDs were diagnosed after age 60. Future analyses with longitudinal measures of the studied biomarkers from middle until old age are warranted to confirm our results. Fourth, we were unable to account for the number of healthcare visits prior to diagnosis in our analysis, as none of our databases included comprehensive healthcare data across all settings (primary, outpatient, and inpatient care). However, since healthcare visits tend to increase shortly before the diagnosis of NDDs, the analysis of the 5- to 10-year period before diagnosis is unlikely to be significantly biased by this factor. Additionally, we were unable to analyse if over-the-counter medication use is associated with future diagnosis of NDDs due to the lack of such information. Furthermore, the information on potential confounders such as genetic and familial environmental factors, lifestyle factors, etc. was not available in the databases used in this study. We calculated E-values to evaluate the robustness of results regarding psychoanaleptics,⁽³⁵⁾ which were consistently associated with AD, PD, and ALS. The E-values for psychoanaleptics in ALS [1.11 (1.04-1.19)] were 1.46 for the point estimate and 1.24 for the upper confidence limit. This indicates that an unmeasured confounder would need to be associated with psychoanaleptics and ALS with a minimum IRR of 1.24 to account for the observed association. While it is possible that certain unmeasured confounders may

contribute to this relationship, substantially stronger confounding effects would be required to account for the associations between psychoanaleptics and AD or PD.

Conclusion

Conducting longitudinal studies across various health registries and diseases is both feasible and valuable. Our large-scale study leveraging data from four countries indicates that depression and psychoanaleptics may serve as predictors for a subsequent diagnosis of AD, PD, and ALS in 5-10 years. Additionally, our findings highlight constipation and related medications as potential indicators for a higher subsequent risk of AD and PD, while diabetes and antidiabetics emerge as potential indicators for a lower risk of ALS. Our findings have practical implications for the development of targeted interventions, laying the groundwork for a more integrated comprehension of the intricate prodromal phases of NDDs with the goal of influencing future research and clinical management strategies. Future studies should look at ATC sub-classes and individual drugs to identify candidates for repurposing.

Contributors

DW, AF, OG, NRW, SD, AM, BCD, FF, and TN design the study. SD, AM, and FF supervised the study. DW, AF, OG, and TN performed formal analysis. DW, OG, TN, and KZ prepared tables and figures. DW, TN, and AM have accessed and verified the underlying data. DW and TN wrote the first draft of the manuscript and all authors contributed to and edited the manuscript. All authors read and approved the final version of the manuscript.

Data Sharing Statement

The data from the SNDS (France) are governed by Articles R. 1461–11 to R. 1461-17 of the French Public Health Code and the French data protection authority decision CNIL-2016-316,

and cannot be shared publicly. Access to the CNAM data portal is restricted to the ARAMIS team through the INRIA affiliation, in compliance with the regulations.

The Australian and THIN data used in this study were obtained from the Australian Institute of Health and Welfare (linkage@aihw.gov.au) and the Cegedim company (info@the-healthimprovement-network.co.uk), respectively.

The Swedish data are register-based data that are pseudonymised and thus subject to General Data Protection Regulation (GDPR) and cannot be shared openly. Underlying data from the AMORIS cohort can be made available upon request to the Research Data Office at Karolinska Institutet via rdo@ki.se after ensuring compliance with relevant legislation and GDPR. The data for analysing medications and health conditions are available for research purposes to qualified researchers upon request to the Swedish National Board of Health and Welfare and Statistics Sweden, provided they meet specific requirements.

The code for meta-analysis is available at https://github.com/thomasnedelec/meta_lemerend.

Declaration of interests

All authors declare no competing interests.

Acknowledgements

This work and the group of contributors were supported by EU Joint Programme – Neurodegenerative Disease Research (grant number: ANR-21-JPW2-0002-01; grant number at Swedish Research Council: 2021-00696), the Australian National Health and Medical Research Council (grant number: 1113400), the “Investissements d’avenir” program, reference ANR-10-IAIHU-06 (Agence Nationale de la Recherche-10-IA Institut Hospitalo-Universitaire-6) and reference ANR-19-P3IA-0001 (PRAIRIE 3IA Institute), the European Union H2020 program (project EuroPOND, grant number: 666992), the joint NSF/NIH/ANR

program “Collaborative Research in Computational Neuroscience” (project HIPLAY7, grant number: ANR-16-NEUC-0001-01), the ICM Big Brain Theory Program (project DYNAMO, project PredictICD), and the Abeona Foundation (project Brain@Scale). The consortium was responsible for data access, data harmonizations, methodological supports, and regular workshops and meetings. BCD is funded by the Australian National Health and Medical Research Council CJ Martin fellowship (grant number: 1161356).

References

1. Gustavsson A, Svensson M, Jacobi F, Allgulander C, Alonso J, Beghi E, et al. Cost of disorders of the brain in Europe 2010. *Eur Neuropsychopharmacol.* 2011;21(10):718-79.
2. GBD, 2016 Neurology Collaborators. Global, regional, and national burden of neurological disorders, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol.* 2019;18(5):459-80.
3. GBD, 2016 Parkinson's Disease Collaborators. Global, regional, and national burden of Parkinson's disease, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol.* 2018;17(11):939-53.
4. GBD, 2019 Dementia Forecasting Collaborators. Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: an analysis for the Global Burden of Disease Study 2019. *Lancet Public Health.* 2022;7(2):e105-e25.
5. Ding C, Wu Y, Chen X, Chen Y, Wu Z, Lin Z, et al. Global, regional, and national burden and attributable risk factors of neurological disorders: The Global Burden of Disease study 1990-2019. *Front Public Health.* 2022;10:952161.
6. Romanowska J, Bjornevik K, Cortese M, Tuominen JA, Solheim M, Abolpour Mofrad A, et al. Association Between Use of Any of the Drugs Prescribed in Norway and the Subsequent Risk of Parkinson Disease: A Drug-wide Association Study. *Neurology.* 2023;101(21):e2068-e77.
7. You J, Guo Y, Wang YJ, Zhang Y, Wang HF, Wang LB, et al. Clinical trajectories preceding incident dementia up to 15 years before diagnosis: a large prospective cohort study. *Mol Psychiatry.* 2024.
8. Bohlken J, Schrag A, Riedel-Heller S, Kostev K. Identification of Prodromal Presentations of Parkinson's Disease among Primary Care Outpatients in Germany. *Neuroepidemiology.* 2022;56(1):41-9.
9. Nedelec T, Couvy-Duchesne B, Monnet F, Daly T, Ansart M, Gantzer L, et al. Identifying health conditions associated with Alzheimer's disease up to 15 years before diagnosis: an agnostic study of French and British health records. *The Lancet Digital Health.* 2022;4(3):e169-e78.
10. Feldman AL, Johansson AL, Gatz M, Flensburg M, Petzinger GM, Widner H, et al. Accuracy and sensitivity of Parkinsonian disorder diagnoses in two Swedish national health registers. *Neuroepidemiology.* 2012;38(3):186-93.
11. Rizzuto D, Feldman AL, Karlsson IK, Dahl Aslan AK, Gatz M, Pedersen NL. Detection of Dementia Cases in Two Swedish Health Registers: A Validation Study. *J Alzheimers Dis.* 2018;61(4):1301-10.
12. Longinetti E, Regodón Wallin A, Samuelsson K, Press R, Zachau A, Ronnevi LO, et al. The Swedish motor neuron disease quality registry. *Amyotroph Lateral Scler Frontotemporal Degener.* 2018;19(7-8):528-37.
13. Röver C, Knapp G, Friede T. Hartung-Knapp-Sidik-Jonkman approach and its modification for random-effects meta-analysis with few studies. *BMC Med Res Methodol.* 2015;15:99.
14. Int'Hout J, Ioannidis JP, Borm GF. The Hartung-Knapp-Sidik-Jonkman method for random effects meta-analysis is straightforward and considerably outperforms the standard DerSimonian-Laird method. *BMC Med Res Methodol.* 2014;14:25.
15. Logroscino G, Marin B, Piccininni M, Arcuti S, Chiò A, Hardiman O, et al. Referral bias in ALS epidemiological studies. *PLoS One.* 2018;13(4):e0195821.
16. GBD, 2016 Motor Neuron Disease Collaborators. Global, regional, and national burden of motor neuron diseases 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol.* 2018;17(12):1083-97.
17. Biétry FA, Pfeil AM, Reich O, Schwenkglens M, Meier CR. Benzodiazepine Use and Risk of Developing Alzheimer's Disease: A Case-Control Study Based on Swiss Claims Data. *CNS Drugs.* 2017;31(3):245-51.

18. 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(1):57-64.
19. Roos E, Mariosa D, Ingre C, Lundholm C, Wirdefeldt K, Roos PM, et al. Depression in amyotrophic lateral sclerosis. *Neurology.* 2016;86(24):2271-7.
20. Turner MR, Goldacre R, Talbot K, Goldacre MJ. Psychiatric disorders prior to amyotrophic lateral sclerosis. *Ann Neurol.* 2016;80(6):935-8.
21. Diniz BS, Teixeira AL, Cao F, Gildengers A, Soares JC, Butters MA, et al. History of Bipolar Disorder and the Risk of Dementia: A Systematic Review and Meta-Analysis. *Am J Geriatr Psychiatry.* 2017;25(4):357-62.
22. Kuusimäki T, Al-Abdulrasul H, Kurki S, Hietala J, Hartikainen S, Koponen M, et al. Increased Risk of Parkinson's Disease in Patients With Schizophrenia Spectrum Disorders. *Mov Disord.* 2021;36(6):1353-61.
23. Faustino PR, Duarte GS, Chendo I, Castro Caldas A, Reimão S, Fernandes RM, et al. Risk of Developing Parkinson Disease in Bipolar Disorder: A Systematic Review and Meta-analysis. *JAMA Neurol.* 2020;77(2):192-8.
24. Cai L, Huang J. Schizophrenia and risk of dementia: a meta-analysis study. *Neuropsychiatr Dis Treat.* 2018;14:2047-55.
25. Nedelec T, Couvy-Duchesne B, Darves-Bornoz A, Couronne R, Monnet F, Gantzer L, et al. A Comparison Between Early Presentation of Dementia with Lewy Bodies, Alzheimer's Disease, and Parkinson's Disease: Evidence from Routine Primary Care and UK Biobank Data. *Ann Neurol.* 2023;94(2):259-70.
26. Cui C, Sun J, McKay KA, Ingre C, Fang F. Medication use and risk of amyotrophic lateral sclerosis-a systematic review. *BMC Med.* 2022;20(1):251.
27. Aune D, Schlesinger S, Mahamat-Saleh Y, Zheng B, Udeh-Momoh CT, Middleton LT. Diabetes mellitus, prediabetes and the risk of Parkinson's disease: a systematic review and meta-analysis of 15 cohort studies with 29.9 million participants and 86,345 cases. *European Journal of Epidemiology.* 2023;38(6):591-604.
28. Biessels GJ, Staekenborg S, Brunner E, Brayne C, Scheltens P. Risk of dementia in diabetes mellitus: a systematic review. *Lancet Neurol.* 2006;5(1):64-74.
29. Livingston G, Huntley J, Sommerlad A, Ames D, Ballard C, Banerjee S, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *Lancet.* 2020;396(10248):413-46.
30. Sundbøll J, Szépligeti SK, Szentkúti P, Adelborg K, Horváth-Puhó E, Pedersen L, et al. Risk of Parkinson Disease and Secondary Parkinsonism in Myocardial Infarction Survivors. *J Am Heart Assoc.* 2022;11(5):e022768.
31. Maheshwari P, Eslick GD. Bacterial infection and Alzheimer's disease: a meta-analysis. *J Alzheimers Dis.* 2015;43(3):957-66.
32. Wang H, Liu X, Tan C, Zhou W, Jiang J, Peng W, et al. Bacterial, viral, and fungal infection-related risk of Parkinson's disease: Meta-analysis of cohort and case-control studies. *Brain Behav.* 2020;10(3):e01549.
33. Joh HK, Kwon H, Son KY, Yun JM, Cho SH, Han K, et al. Allergic Diseases and Risk of Incident Dementia and Alzheimer's Disease. *Ann Neurol.* 2023;93(2):384-97.
34. Nam JY, Park SJ, Song J, Jeong S, Choi S, Park SM. Association of allergic disease with Parkinson's disease: A nationally representative retrospective cohort study. *Allergol Int.* 2024;73(1):107-14.
35. Haneuse S, VanderWeele TJ, Arterburn D. Using the E-Value to Assess the Potential Effect of Unmeasured Confounding in Observational Studies. *Jama.* 2019;321(6):602-3.

Table and figure legends

Table 1. Characteristics of individuals with Alzheimer's disease, Parkinson's disease, or amyotrophic lateral sclerosis and their individually matched controls in Australia, France, the UK, and Sweden

Table 2. Risk ratios and 95% confidence intervals of Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis in relation to blood biomarkers in Sweden

Figure 1. Summary of study design and results for investigating the associations of prescribed medications, health conditions, and blood biomarkers with the subsequent diagnosis of Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis in Australia, France, the UK, and Sweden

Figure 2. Prescribed medications associated with the subsequent diagnosis of Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis during 5-10 years before the diagnosis, meta-analyses from Australia, France, the UK, and Sweden

Figure 3. Health conditions associated with the subsequent diagnosis of Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis during 5-10 years before the diagnosis, meta-analyses from France, the UK, and Sweden

Table 1. Characteristics of individuals with Alzheimer’s disease, Parkinson’s disease, or amyotrophic lateral sclerosis and their individually matched controls in Australia, France, the UK, and Sweden

Characteristics	Alzheimer’s disease				Parkinson’s disease			Amyotrophic lateral sclerosis			
	France	The UK	Sweden 1	Sweden 2	France	Sweden 1	Sweden 2	Australia	France	Sweden 1	Sweden 2
N of cases/controls	19,458/ 19,458	20,214/ 20,214	109,881/ 1,098,810	39,341/ 393,410	195,575/ 195,575	57,121/ 571,210	18,209/ 182,090	6621/ 66,210	14,065/ 140,650	6847/ 68,470	3062/ 30,620
Age at diagnosis, mean (SD)	79.1 (10.0)	80.9 (8.4)	81.2 (8.0)	81.1 (8.3)	73.2 (9.7)	75.9 (9.7)	74.7 (10.4)	64.4 (11.9)	67.5 (12.5)	69.7 (12.1)	69.6 (12.2)
Sex, N (%)											
Men	7016 (37.0)	6108 (31.0)	40,686 (37.0)	15181 (38.6)	111,223 (56.9)	32,630 (57.1)	10,850 (59.6)	3956 (59.7)	7803 (54.5)	3825 (55.9)	1686 (55.1)
Women	12,442 (63.0)	14,106 (69.0)	69,195 (63.0)	24160 (61.4)	84,352 (43.1)	24,491 (42.9)	7359 (40.4)	2665 (40.3)	6262 (45.5)	3022 (44.1)	1376 (44.9)
Year of diagnosis, N (%)											
<1990	0	11 (0.05)	14,683 (13.4)	0	0	5677 (9.9)	0	0	0	469 (6.8)	0
1990-1999	17 (0.09)	2045 (10.1)	31,893 (29.0)	0	0	17,652 (30.9)	0	0	0	1605 (23.4)	0
2000-2009	9247 (47.5)	10,602 (52.4)	35,579 (32.4)	11,615 (29.5)	0	21,291 (37.3)	5708 (31.3)	2432 (36.7)	0	2537 (37.1)	826 (27.0)
≥2010	10,194 (53.4)	7556 (37.4)	27,726 (25.2)	27,726 (70.5)	195,575 (100)	12,501 (21.9)	12,501 (68.7)	4189 (63.3)	14,065 (100)	2236 (32.7)	2236 (73.0)
Years of data before diagnosis, mean (SD)	7.5 (4.3)	13.1 (6.2)	37.9 (9.3)	7.1 (2.9)	8.2 (2.3)	37.9 (8.5)	6.9 (2.9)	10.3 (4.5)	8.2 (2.2)	40.4 (8.5)	7.3 (2.9)

Sweden 1: Cases included in the analysis of health conditions; Sweden 2: Cases included in the analysis of prescribed medications.

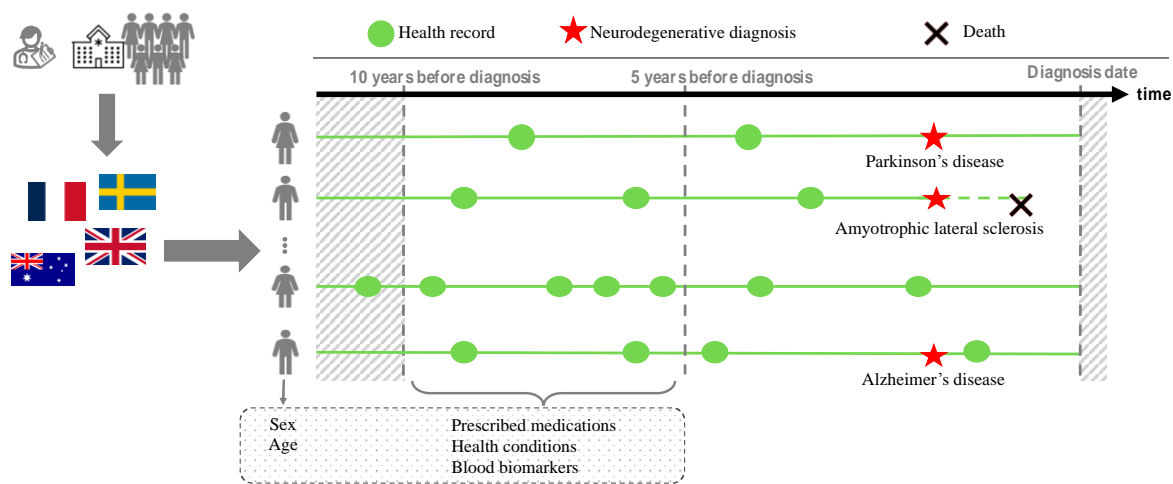
Table 2. Risk ratios and 95% confidence intervals of Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis in relation to blood biomarkers in Sweden [□]

Biomarkers	Reference values	5-10 years before the diagnosis			>10 years before the diagnosis		
		Alzheimer's disease	Parkinson's disease	Amyotrophic lateral sclerosis	Alzheimer's disease	Parkinson's disease	Amyotrophic lateral sclerosis
Apolipoprotein A (ApoA)	Male: <2 g/L; Female: <2.3 g/L	0.28 (0.01-6.42)	1.37 (0.16-11.99)	- [†]	1.24 (0.69-2.22)	0.66 (0.23-1.85)	1.39 (0.12-16.13)
Apolipoprotein B (ApoB)	Male: <1.3 g/L; Female: <1.5 g/L	0.87 (0.58-1.29)	0.60 (0.37-0.97)	0.69 (0.19-2.55)	1.13 (1.01-1.25)	0.85 (0.72-1.00)	0.92 (0.59-1.45)
Ratio of ApoB/ApoA	Male: <0.8; Female: <0.7 g/L	0.83 (0.56-1.24)	0.80 (0.49-1.31)	1.41 (0.33-6.06)	1.16 (1.04-1.30)	0.91 (0.76-1.09)	1.15 (0.71-1.88)
High-density lipoprotein (HDL)	Male: <2.1 mmol/L; Female: <2.7 mmol/L	1.23 (0.55-2.75)	0.75 (0.25-2.26)	0.60 (0.06-6.21)	1.02 (0.80-1.31)	0.79 (0.55-1.15)	0.74 (0.23-2.35)
Low-density lipoprotein (LDL)	Male: <5.3 mmol/L; Female: <5.3 mmol/L	0.87 (0.53-1.42)	0.73 (0.37-1.46)	0.77 (0.16-3.71)	1.17 (1.02-1.35)	0.87 (0.67-1.12)	1.07 (0.54-2.09)
Ratio of LDL/HDL	Male: <2.5; Female: <2.5	0.93 (0.69-1.26)	0.77 (0.52-1.14)	1.08 (0.42-2.78)	1.13 (1.03-1.23)	0.93 (0.81-1.06)	1.00 (0.69-1.47)
Total cholesterol	Male: <7.8 mmol/L; Female: <7.8 mmol/L	0.98 (0.72-1.35)	0.83 (0.52-1.32)	0.74 (0.24-2.30)	1.06 (0.94-1.18)	0.88 (0.71-1.08)	1.42 (0.86-2.35)
Triglycerides	Male: <2.6 mmol/L; Female: <2.6 mmol/L	0.69 (0.50-0.95)	0.70 (0.47-1.03)	1.00 (0.47-2.10)	1.06 (0.96-1.17)	0.79 (0.67-0.92)	0.96 (0.63-1.44)
Glucose	Male: <7 mmol/L; Female: <7 mmol/L	0.83 (0.59-1.18)	0.78 (0.51-1.21)	0.59 (0.14-2.50)	1.05 (0.91-1.21)	0.97 (0.78-1.22)	0.53 (0.21-1.33)

Creatinine	Male: <105 $\mu\text{mol/L}$; Female: <90 $\mu\text{mol/L}$	0.86 (0.69-1.07)	1.04 (0.78-1.39)	1.12 (0.49-2.55)	0.92 (0.83-1.02)	1.09 (0.92-1.28)	0.96 (0.58-1.58)
Leukocyte	Male: <8.8 $\times 10^9/\text{L}$; Female: <8.8 $\times 10^9/\text{L}$	0.74 (0.50-1.10)	0.79 (0.45-1.40)	1.75 (0.45-6.81)	0.92 (0.77-1.09)	0.69 (0.51-0.94)	1.26 (0.54-2.94)
Haptoglobin	Male: <1.9 g/L; Female: <1.9 g/L	0.54 (0.25-1.15)	0.82 (0.30-2.21)	0.91 (0.18-4.71)	0.83 (0.64-1.08)	0.94 (0.61-1.44)	1.14 (0.34-3.78)
C-reactive protein	Male: <5 mg/L; Female: <5 mg/L	0.85 (0.66-1.09)	0.89 (0.65-1.22)	1.70 (0.82-3.52)	0.95 (0.87-1.02)	1.02 (0.90-1.15)	0.99 (0.71-1.38)

□ Adjusted for sex, country of birth, calendar year of blood sampling, calendar year of the index date, and age at the index date.

† All cases of amyotrophic lateral sclerosis had the level of apolipoprotein A higher than 2 g/L (male) or 2.3 g/L (female) during 5-10 years before diagnosis.



Alzheimer's disease

	Prescribed medications			Health conditions			Blood biomarkers
Countries							
Period	1998-2019	1996-2020	2006-2016	1998-2019	1996-2020	1987-2016	1987-2016
Cases	19,458	20,214	43,258	19,458	20,214	109,881	22,294
Controls	19,458	20,214	432,580	19,458	20,214	1,098,810	222,940
Meta-analysis	49 drugs			73 health conditions			13 biomarkers
Significant associations during 5-10 years before diagnosis	12 drugs			11 health conditions			4 biomarkers*

Parkinson's disease

	Prescribed medications		Health conditions		Blood biomarkers
Countries					
Period	2014-2022	2006-2016	2014-2022	1987-2016	1987-2016
Cases	195,575	20,078	195,575	57,121	9000
Controls	195,575	200,780	195,575	571,210	90,000
Meta-analysis	45 drugs		134 health conditions		13 biomarkers
Significant associations during 5-10 years before diagnosis	20 drugs		25 health conditions		3 biomarkers*

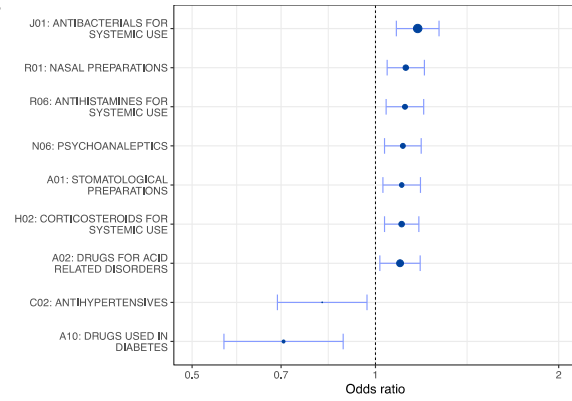
Amyotrophic lateral sclerosis

	Prescribed medications			Health conditions			Blood biomarkers
Countries							
Period	2002-2018	2014-2022	2006-2016	2014-2022	1987-2016	1987-2016	
Cases	6621	14,065	3290	14,065	6847	1215	
Controls	66,210	140,650	32,900	140,650	68,470	12,150	
Meta-analysis	43 drugs			131 health conditions			13 biomarkers
Significant associations during 5-10 years before diagnosis	8 drugs			5 health conditions			0 biomarkers*

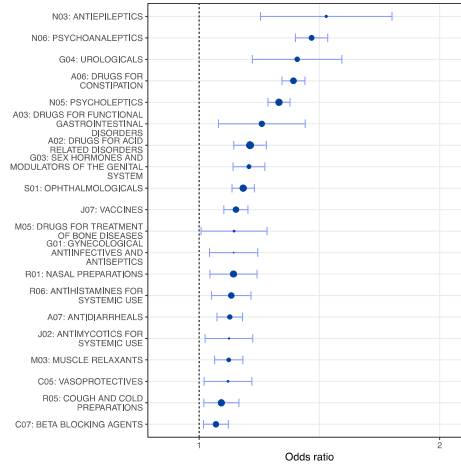
*As blood biomarkers were measured at midlife (mean: 43 years), we reported the results of biomarkers measured >10 years before diagnosis.

Figure 1. Summary of study design and results for investigating the associations of prescribed medications, health conditions, and blood biomarkers with the subsequent diagnosis of Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis in Australia, France, the UK, and Sweden

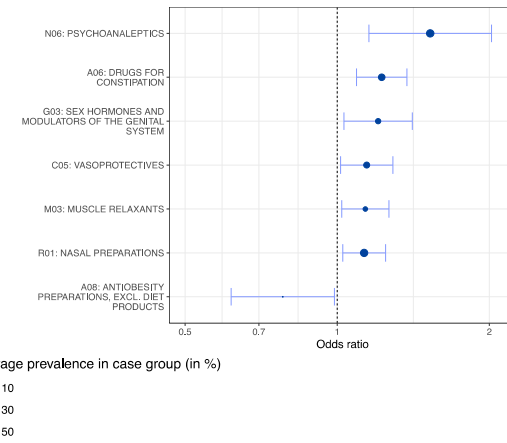
a. Associations with ALS (5-10 years before diagnosis)



b. Associations with PD (5-10 years before diagnosis)



c. Associations with AD (5-10 years before diagnosis)



d. Comparison between neurodegenerative diseases (5-10 years before diagnosis)

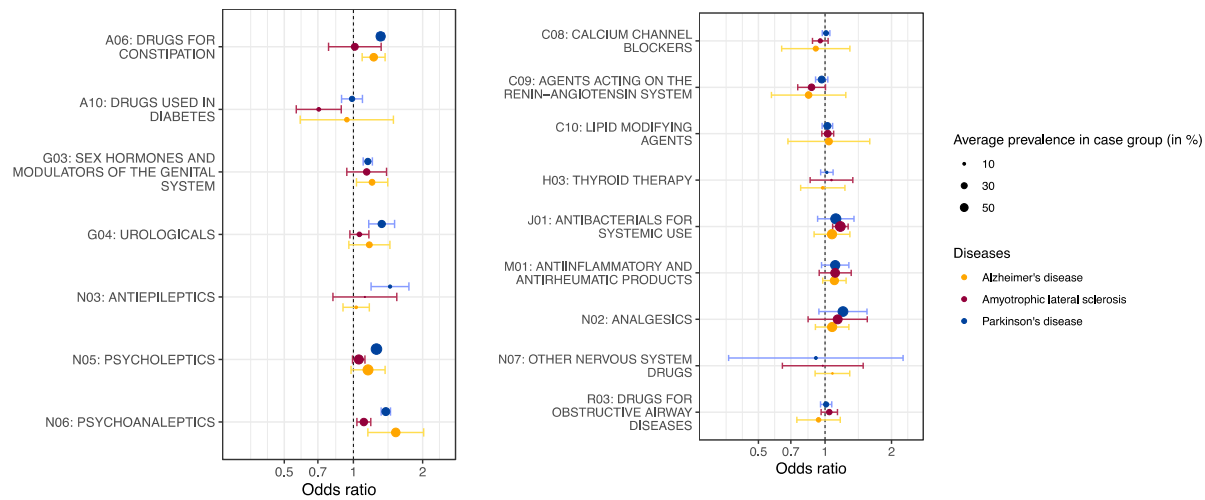
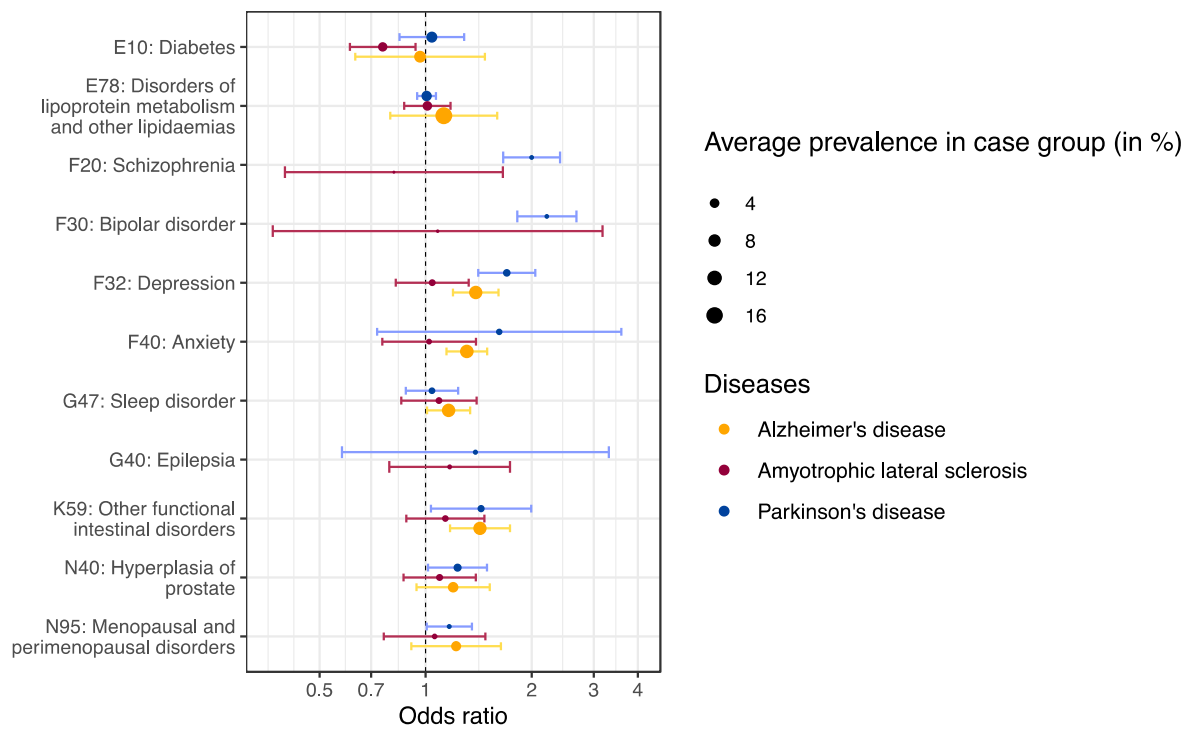


Figure 2. Prescribed medications associated with the subsequent diagnosis of Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis during 5-10 years before the diagnosis, meta-analyses from Australia, France, the UK, and Sweden. AD=Alzheimer's disease; ALS=amyotrophic lateral sclerosis; PD=Parkinson's disease. Only classes of medications with an odds ratio from the meta-analysis above 1.2 or below 0.8 which was statistically significant in at least one of three diseases are shown in panel d. The size of the dot is proportional to the number of cases. Bars correspond to 95% confidence intervals in the meta-analysis after correction for multiple testing.

Associations with neurodegenerative diseases (5-10 years before diagnosis)



1

2 **Figure 3. Health conditions associated with the subsequent diagnosis of Alzheimer's**
 3 **disease, Parkinson's disease, and amyotrophic lateral sclerosis during 5-10 years before**
 4 **the diagnosis, meta-analyses from France, the UK, and Sweden.** Health conditions
 5 presented in this figure are related to the prescribed medications that were associated with the
 6 neurodegenerative diseases shown in Figure 2.

7

8

9

10

11