Chronic diseases and multimorbidity patterns, their recent onset, and risk of new-onset Parkinson's disease and related functional degeneration in older adults: a prospective cohort study

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Summary

Background Certain chronic diseases contribute to increased risks of Parkinson's disease (PD), but the association between time-varying multimorbidity patterns and new-onset PD remains underexplored.

Methods Data were from the Survey of Health, Ageing and Retirement in Europe (SHARE) waves 5–8 conducted between January 2013 and March 2020. Eleven chronic diseases were included, with ≥2 denoting multimorbidity. Three multimorbidity patterns were further defined: somatic multimorbidity (SMM), neuropsychiatric multimorbidity (NPM), and cardiometabolic multimorbidity (CMM). PD-related function degeneration included functional limitations, mobility limitations, depressive symptoms, and cognitive decline. Time-dependent analyses, competing-risk analyses, and mixed-effect models were utilised.

Findings In this prospective cohort study, 557 developed new-onset PD during follow-ups among 64,273 participants included at baseline, as defined by participants' self-reported physician diagnoses. Participants with (vs. without) multimorbidity, SMM, NPM, and CMM were at 1.40–2.70 times higher PD risk after considering the competing role of all-cause death, which remained significant in all sensitivity analyses and were more pronounced in lower-income participants (P for interaction <0.05). Similarly, they tended to develop functional degeneration faster than those without these multimorbidity patterns (P < 0.05). Participants with recent-onset (newly diagnosed in 2015) multimorbidity patterns were at 1.45–3.72 times higher risk of PD than those never diagnosed. Interestingly, they were at comparable or even higher (though P values for >0.05) PD risk compared to participants with multimorbidity patterns diagnosed in 2013 or before. Furthermore, recent-onset (vs. prior diagnosed) NPM exhibited faster functional deterioration and cognitive decline (P for difference <0.05).

Interpretation Our findings suggest that promoting early prevention of multimorbidity, especially recent-onset multimorbidity and NPM, could prevent some subsequent cases of PD and related functional degeneration among older adults. However, further studies are needed to confirm this association.

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Keywords: Chronic disease; Multimorbidity; Time-dependent; Parkinson's disease; Functional degeneration

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Research in context

Evidence before this study

We searched PubMed and Web of Science with the terms (chronic disease or chronic condition or multimorbidity) and ("Parkinson's disease" or Parkinson* or Parkinsonism*) with no date or language restrictions for articles published before June 1, 2023. Despite positive associations between certain chronic diseases and new-onset Parkinson's disease (PD), prior evidence on multimorbidity and different multimorbidity patterns was limited. Furthermore, one major limitation of previous studies was the inadequate consideration of the time-dependent changes in chronic conditions among older adults. Given the progressive nature of PD and the rapidly rising prevalence of multimorbidity, further exploration of the association between recent-onset multimorbidity and the risk of PD was also warranted but remained unclear.

Added value of this study

To our knowledge, this is the first prospective cohort study identifying positive associations of time-varying distinct chronic diseases and multiple multimorbidity patterns with increased risks of PD and PD-related functional degeneration among older adults after considering the competing risk of all-cause death. Compared to those with prior diagnosed corresponding conditions, participants with certain recent-onset chronic diseases or multimorbidity patterns, especially those neuropsychiatric-related, were at comparable or even higher risk of new-onset PD and exhibited faster deterioration in daily function and cognitive function. Potential key intervention populations, namely, lower-income and single older adults were also identified.

Implications of all the available evidence

Our findings call for early detection and effective management of multimorbidity in the prevention of PD and functional degeneration, especially for old adults with recent-onset neuropsychiatric multimorbidity. Furthermore, more diverse instruments beyond functional degeneration are warranted to capture PD risk exactly.

Introduction

Parkinson's disease (PD) refers to a neurodegenerative disorder characterised by tremors and bradykinesia, which has affected an increasing number of individuals from 2.5 million to 6.1 million during the past three decades.[1,2] In addition to typical symptoms, functional degeneration, including limitations in daily life and mobility, as well as neuropsychiatric complications like depressive symptoms and cognitive decline, are common before and after the onset of PD.[3,4]

Due to population ageing, multimorbidity, which refers to the coexistence of multiple chronic diseases, has evolved into a serious public health concern and now poses significant challenges for older adults, caregivers, and society.[5] Distinct chronic diseases and multimorbidity patterns exhibit diverse pathological mechanisms and divergent long-term impacts on the health outcomes of older adults.[6] Consequently, investigating the association of specific chronic diseases and multimorbidity patterns with subsequent health outcomes can help identify targeted primary prevention strategies to address health risks.

Previous research has indicated positive associations between certain chronic conditions, such as cardiometabolic diseases, arthritis, and depressive symptoms, and new-onset PD.[7–10] However, evidence on other chronic diseases, such as digestive diseases, lung diseases, and cataracts, has not been examined in detail. Given that approximately one-third of adults worldwide exhibit two or more chronic diseases,[5] further investigation of the association between multimorbidity and the onset of PD and its related functional degeneration is of substantial practical importance. Conducting comprehensive investigations into the association between diverse multimorbidity patterns, such as somatic and neuropsychiatric conditions, and new-onset PD also holds profound implications for developing clinical screening strategies targeted for PD. Nevertheless, evidence on this topic is currently limited. Given the progressive nature of PD and the rapidly rising prevalence of multimorbidity, further exploration of the association between recent-onset multimorbidity and the risk of PD and related functional degeneration is warranted, though currently limited in research.

To bridge these knowledge gaps, we conducted a prospective cohort study to examine the longitudinal associations of various chronic diseases, different multimorbidity patterns, and their recent onset with subsequent risk of new-onset PD and PD-related function degeneration in older European adults, based on a cohort dataset across numerous European countries.

Methods

Study population and ethics

In this study, we utilised data from the Survey of Health, Ageing and Retirement in Europe (SHARE), which is a multicentre panel survey covering community-dwelling individuals aged 50 years and above across twenty-seven European countries and Israel.[11] The survey biennially collects information on various facets of participants' lives, including health status, socioeconomic factors, and familial and social networks. The SHARE was reviewed and approved by the Ethics Council of the Max Planck Society and the Ethics Councils of the participating countries. All of the study's participants provided informed consent before inclusion in the research. Our analysis utilised SHARE waves 5–8

conducted between January 2013 and March 2020.[12–15] The baseline was set as wave 5, with follow-ups in waves 6–8 conducted starting in 2015, 2017, and 2019. For clarity, the starting years of the waves in SHARE were used to indicate them in this manuscript.

The study flowchart is shown in Figure S1. Of the 65,052 participants aged 50 or older in 2013, those who had missing data on the history of chronic diseases (N = 222) and who had prior PD (N = 557) were excluded, leaving 64,273 participants.

Definition of chronic diseases and different multimorbidity patterns

Eleven chronic diseases, including hypertension, diabetes, dyslipidaemia, heart diseases, stroke, lung diseases, digestive diseases, cataracts, rheumatoid arthritis or osteoporosis, affective disorders, and dementia, were defined by participants' self-reported physician diagnoses or treatments at each wave. Of them, affective disorders and dementia were further classified as neuropsychiatric diseases, while others were classified as somatic diseases. Hypertension, diabetes, dyslipidaemia, heart diseases, and stroke were further classified as cardiometabolic diseases.

Multimorbidity referred to the coexistence of two or more chronic diseases; somatic multimorbidity (SMM) included the coexistence of two or more somatic diseases; neuropsychiatric multimorbidity (NPM) involved the coexistence of both affective disorders and dementia; and cardiometabolic multimorbidity (CMM) encompassed the coexistence of two or more cardiometabolic diseases.

Definition of PD and all-cause death

PD was defined by participants' self-reported physician diagnosis at each wave. All-cause death was confirmed by proxy respondents, such as family members, household members, or neighbours, during follow-ups.

Definition of PD-related functional degeneration

PD-related functional degeneration, namely, functional limitations, mobility limitations, depressive symptoms, and cognitive decline, were included in this study to help interpret the associations with PD. All the functional degeneration in the SHARE has been validated and widely used by the scientific community.

Functional limitations referred to any limitations in activities of daily living (ADL) or instrumental activities of daily living (IADL), which have been widely applied worldwide. ADLs referred to six items,[16] including dressing, walking across a room, bathing, eating, getting in or out of bed, and using the toilet. IADL referred to seven items,[17] such as using a map, preparing a hot meal, shopping, making telephone calls, taking medications, doing work around the house or garden, and managing money. More limitations in ADLs or IADLs indicated more functional limitations.

The SHARE also asked participants whether they had limitations in ten mobility items, including six in mobility ("Walking 100 m", "Sitting for about 2 h", "Getting up from a chair after sitting for long periods", "Climbing several flights of stairs without resting", "Climbing one flight of stairs without resting", and "Stooping, kneeling, or crouching"), three in arm function ("Reaching or extending your arms above shoulder level", "Pulling or pushing large objects like a living room chair", and "Lifting or carrying weights over 10 pounds/5 kilos, like a heavy bag of groceries"), and one in fine motor ("Picking up a small coin from a table"). These ten mobility-related questions were an extended version of previous mobility sensory functioning questions and have been widely used in previous studies.[18,19] Having limitations in more items indicated more mobility limitations.

Depressive symptoms were measured using the Europe-depression (EURO-D) scale, which assessed 12 emotional states experienced by respondents within the past month, including depressed mood, pessimism, suicidal tendencies, guilt, sleep, interest, irritability, appetite, fatigue, concentration, enjoyment, and tearfulness. Each item was rated on a scale of 0 or 1, resulting in an overall score ranging from 0 to 12. The reliability and validity of the EURO-D scale have been extensively confirmed in European countries.[20] Higher EURO-D scores referred to more depressive symptoms.

Cognitive function in the SHARE included three domains: verbal fluency, episodic memory, and numeracy. The verbal fluency was assessed by asking respondents to list as many unique animals as they could within a 60-s time frame, which can reflect executive functioning and language ability.[21] Episodic memory was determined by the sum of immediate and delayed word recalls using ten random words, which was adapted from the modified Telephone Interview of Cognitive Status (TICS).[22] The numeracy was measured using serial-7 number subtraction questions, which referred to five serial subtractions of 7 from 100 (0–5) and can reflect concentration and basic calculation skills.[23] A higher cognitive score referred to better cognitive function.

Subsequently, the total depressive scores and cognitive scores in 2013 were calculated as each-5-year-age stratified z scores, while scores in 2015, 2017, and 2019 were converted to z scores based on the means and standard deviations in 2013.

Definition of covariates

Information on demographic, socioeconomic, lifestyle, and health-related characteristics in the SHARE was collected using questionnaires by professional health workers.

Age was calculated by subtracting birth year from interview year. Six social determinants of health (SDoH) were identified in this study, including sex, residence,

education, occupation, household income, and marital status. Sex is identified by biological characteristics, not self-identity, including men and women. Residence was classified as rural and urban. Education referred to the highest degree completed by the participants and was categorised as less than high school, high school, and college or above. Occupation was classified as employed or self-employed, retired, and others. Household income was calculated by gross household income each month and was divided into bottom, middle, and top tertiles. Marital status was defined as married/cohabiting and single.

Smoking and drinking history were classified as current or not. Irregular physical activity referred to doing moderate and vigorous sports or activities less than once a week. If participants reported not daily serving of fruits or vegetables, they were classified as unhealthy diet. Body mass index was measured by trained health workers. A BMI of 25 kg/m^2 or more was considered abnormal weight.

In the SHARE, participants were asked whether they were bothered by four frailty domains: falling, fear of falling, dizziness, and fatigue. Those who reported any frailty items were classified as frailty. Loneliness was measured using the three-item short form of the Revised UCLA loneliness scale,[24] including "left out, " "isolated from others, " and "lacking companionship", with options of hardly ever or never (assigned as 1), sometimes (assigned as 2), and often (assigned as 3). The total score of loneliness ranged from 3 to 9. Those who scored 6 or more were classified as loneliness.[25]

The history of cancer was determined by participants' self-reported physician diagnosis or treatment. If participants reported using drugs for sleep problems or psychiatric disorders, they were recorded as using psychotropic or sedative medicines. The drugs for high blood pressure, diabetes, high blood cholesterol, coronary diseases and other heart diseases, joint pain and osteoporosis, stomach burns, chronic bronchitis, and suppressing inflammation were classified as other medicines. They were then summed and divided into no, 1, and 2 or more.

Statistical analysis

The baseline characteristics of included participants were described as medians with interquartile ranges (IQRs) for age given its non-normal distribution, and frequency and per cent (%) for categorical variables. Missing data on SDoH, lifestyles, and health-related covariates were presented as "Missing" and were multiply imputed for subsequent analysis. To compare the differences in age and categorical variables between participants with and without new-onset PD during the follow-up period, the Mann–Whitney U test and Chi-square tests were utilised, respectively.

The incidence density of PD and all-cause mortality in participants free of or suffering from chronic diseases or multimorbidity were presented as events per 10^5 person-years. Competing-risk analyses based on subdistribution and cause-specific hazard models were used to explore the associations of chronic diseases and multimorbidity patterns in 2013 with new-onset PD during 2013∼2019, respectively, with all-cause death as the competing event.

The competing risk analysis is an extension of the conventional Cox proportional hazards model. The latter assumes that participants who continue to be followed up are at the same risk for new-onset events as those censored and that if participants had not discontinued their involvement, the outcome of interest would have been eventually observed.[26] A competing risk is an event whose occurrence impacts the risk of the primary event of interest.[27] For instance, in this study, older adults who pass away are no longer at risk of PD and will not be observed to develop PD, thereby violating the assumptions of the conventional Cox proportional hazards model. The competing risk analysis allows for the simultaneous consideration of multiple outcomes, encompassing their temporal correlations and interactions, thereby facilitating a more precise estimation of the risks of each event. The cause-specific hazard model and subdistribution hazard model are typically utilised to deal with competing risks. The former denotes the instantaneous rate of the primary events in participants who are currently event-free and is better suited for addressing epidemiological questions of aetiology, whereas the latter allows estimating covariate effects on cumulative incidence function for the events of interest, serving the purpose of constructing clinical prediction models and risk assessment systems for survival outcomes.[27] In this study, both of them were utilised to ensure the robustness of the findings.

The proportional hazards assumption was verified using scaled Schoenfeld residual tests. Furthermore, time-dependent analyses on time-varying exposure variables (i.e., chronic diseases and multimorbidity) were conducted to capture the changes in chronic conditions in older adults during follow-ups. All models were adjusted for age, sex, residence, education, occupation, household income, marital status, current smoking, current drinking, irregular physical activity, unhealthy diet, abnormal weight, frailty, loneliness, history of cancer, use of psychotropic or sedative medicines, and use of other medicines.

Six sensitivity analyses were conducted to ensure the reliability of our conclusions: First, complete-case analysis without multiple imputation; Second, excluded participants with heart diseases or stroke at baseline or during follow-up to rule out the vascular causes of parkinsonism; Third, excluded participants with dementia at baseline or during follow-up to avoid misdiagnosing dementia as PD; Fourth, defined new-onset PD strictly (i.e., the following situations exist simultaneously: self-reported physician diagnosis, at least one

limitation in ADLs, IADLs, and mobility, depressive z scores of >1.5, and cognitive z scores of <–1.5); Fifth, excluded patients diagnosed with PD in 2015 to account for potential latency time windows and avoid the potential reverse-causality bias; Sixth, further considering countries and survey weights to ensure that the conclusions can be extrapolated from the analytic sample to the population.

Furthermore, SDoH (sex, residence, education, occupation, household income, and marital status)-stratified associations of chronic diseases and multimorbidity with new-onset PD were explored. All models were fully adjusted as those used in the main analysis. The multiplicative interactions between SDoH and chronic diseases/multimorbidity were assessed using their multiplied terms to identify potential effect modifications of SDoH in the associations between chronic diseases/multimorbidity and new-onset PD and distinguish statistically significant differences among groups.

To help interpret our results, fully adjusted competing risk analyses were used to validate ADL limitations, IADL limitations, mobility limitations, depressive symptoms, and cognitive impairment as risk factors for PD. Subsequently, fully adjusted mixed-effect models with random intercepts and slopes were utilised to explore the longitudinal associations of chronic diseases and multimorbidity patterns with the degeneration of ADL/IADL limitations, mobility limitations, depressive symptoms, and cognitive decline during follow-ups. The mixed-effect models are particularly well-suited for handling longitudinal observations with repeated measures. They allow for the simultaneous modelling of individual-level variability (random intercepts) and temporal changes (random slopes). By incorporating random intercepts and slopes, variations in baseline levels and rates of change are accounted for, enabling a more precise capture of inter-individual differences and trends. Additionally, random intercepts and slopes can help control for latent influences arising from unobserved factors, thus ensuring that the observed effects genuinely pertain to the variables of interest. To better capture the emerging deterioration of these PD-related features, participants with PD-related functional impairment (namely, any limitations in ADLs, IADLs, or mobility, depressive z scores of >1.5, or cognitive z scores of <–1.5) were excluded. The exposure variables of corresponding equations were set as chronic diseases/multimorbidity patterns + time + chronic diseases/multimorbidity patterns*time, and we focused on the coefficients of the product term of chronic diseases/multimorbidity patterns and time to characterise the slope of degeneration over time.

Subsequently, participants with full data on chronic diseases and free of PD in 2015 were included to identify the transitions of chronic conditions from 2013 to 2015. The transitions of chronic diseases and multimorbidity patterns were classified as never (never diagnosed in 2013 or 2015), prior diagnosed (diagnosed in 2013 or before), and recent onset (first diagnosed in 2015). The fully adjusted associations of the transitions of chronic diseases and multimorbidity patterns from 2013 to 2015 with new-onset PD from 2015 to 2019 were investigated using competing risk analyses. The differences between prior diagnosed and recent onset groups were assessed using the Wald tests and further adjusted for false discovery rate (FDR) using the Benjamini-Hochberg method to deal with the increased risk of false positives in multiple comparisons (prior diagnosed vs. never, recent onset vs. never, and recent onset vs. prior diagnosed). Furthermore, the associations of the transitions of chronic diseases and multimorbidity patterns from 2013 to 2015 with the slope of PD-related functional degeneration from 2015 to 2019 were investigated using fully adjusted mixed-effect models with random intercepts and slopes in participants without corresponding functional impairment in 2015. The differences between prior diagnosed and recent onset groups were assessed using post hoc multiple comparisons of mixed-effect models based on estimated marginal means and were further FDR-adjusted.

Reporting of this study was done under Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. Analyses were performed using SAS statistical software version 9.4 (SAS Institute) and R statistical software version 4.2.3 (R Project for Statistical Computing). All analyses were two-sided. *P* values of <0.05 or the 95% confidence intervals (CIs) of subdistribution hazard ratio (sHR) and cause-specific hazard ratio (cHR) that did not cross 1.00 were considered statistically significant.

Role of the funding source

All authors had full access to all the data in the study and accepted responsibility for the decision to submit for publication. The funding source had no involvement in the collection, analysis, or interpretation of data; in the writing of the report; or in the decision to submit the paper for publication.

Results

The baseline characteristics of the participants included are shown in Table 1. A total of 64,273 participants (44.5% men) aged 66.0 (59.0–74.0) years were included. Over approximately six years of follow-up, 557 participants (175.3/10^5 person-years) developed new-onset PD, while 9146 (2471.9/10^5 person-years) participants died. Participants who had multimorbidity, SMM, NPM, or CMM at baseline seem to be at higher risk of new-onset PD (all *P* values < 0.05).

Fig. 1 shows that participants with NPM and dementia at baseline exhibit the highest incidence density of PD and all-cause mortality. According to Fig. 2, participants with certain chronic diseases, such as

Characteristics	No new-onset PD (N = 63,716)	New-onset PD (N = 557)	*P* value
Age, year	66.0 (59.0–74.0)	74.0 (68.0–80.0)	<0.001
Sex			0.016
Men	28,311 (44.4)	276 (49.6)	
Women	35,405 (55.6)	281 (50.5)	
Residence			0.004
Rural	19,145 (30.1)	132 (23.7)	
Urban	41,537 (65.2)	400 (71.8)	
Missing	3034 (4.8)	25 (4.5)	
Education			<0.001
Less than high school	24,827 (39.0)	266 (47.8)	
High school	20,554 (32.3)	159 (28.6)	
College or above	17,498 (27.5)	127 (22.8)	
Missing	837 (1.3)	5 (0.9)	
Occupation			<0.001
Employed or self-employed	17,533 (27.5)	42 (7.5)	
Retired	35,652 (56.0)	414 (74.3)	
Others	9770 (15.3)	92 (16.5)	
Missing	761 (1.2)	9 (1.6)	
Household income			<0.001
Bottom tertile	16,811 (26.4)	203 (36.5)	
Middle tertile	16,931 (26.6)	140 (25.1)	
Top tertile	16,821 (26.4)	115 (20.7)	
Missing	13,153 (20.6)	99 (17.8)	
Marital status			0.341
Married/cohabiting	46,560 (73.1)	397 (71.3)	
Single	17,156 (26.9)	160 (28.7)	
Current smoking			<0.001
Yes	11,257 (17.7)	48 (8.6)	
No	52,438 (82.3)	509 (91.4)	
Missing	21 (0.0)	0 (0.0)	
Current drinking			<0.001
Yes	37,208 (58.4)	243 (43.6)	
No	26,461 (41.5)	314 (56.4)	
Missing	47 (0.1)	0 (0.0)	
Irregular physical activity			<0.001
Yes	45,776 (71.8)	333 (59.8)	
No	17,921 (28.1)	224 (40.2)	
Missing	19 (0.0)	0 (0.0)	
Unhealthy diet			0.816
Yes	50,264 (78.9)	436 (78.3)	
No	13,386 (21.0)	120 (21.5)	
Missing	66 (0.1)	1 (0.2)	
Abnormal weight			0.001
Yes	38,448 (60.3)	350 (62.8)	
No	23,643 (37.1)	181 (32.5)	
Missing	1625 (2.6)	26 (4.7)	
Frailty			<0.001
Yes	22,626 (35.5)	297 (53.3)	
No	41,046 (64.4)	258 (46.3)	
Missing	44 (0.1)	2 (0.4)	
Loneliness			<0.001
Yes	7027 (11.0)	97 (17.4)	
No	55,255 (86.7)	441 (79.2)	
Missing	1434 (2.3)	19 (3.4)	

(Table 1 continues on next page)

Characteristics	No new-onset PD (N = 63,716)	New-onset PD (N = 557)	*P* value
(Continued from previous page)			
History of cancer			0.336
Yes	3628 (5.7)	37 (6.6)	
No	60,088 (94.3)	520 (93.4)	
Use of psychotropic or sedative medicines			<0.001
Yes	7741 (12.2)	119 (21.4)	
No	55,911 (87.8)	436 (78.3)	
Missing	64 (0.1)	2 (0.4)	
Use of other medicines			<0.001
No	20,719 (32.5)	94 (16.9)	
1	17,465 (27.4)	137 (24.6)	
2 or more	25,468 (40.0)	324 (58.2)	
Missing	64 (0.1)	2 (0.4)	
Multimorbidity			<0.001
Yes	25,179 (39.5)	323 (58.0)	
No	38,537 (60.5)	234 (42.0)	
SMM			<0.001
Yes	24,002 (37.7)	309 (55.5)	
No	39,714 (62.3)	248 (44.5)	
NPM			<0.001
Yes	223 (0.4)	9 (1.6)	
No	63,493 (99.7)	548 (98.4)	
CMM			<0.001
Yes	15,733 (24.7)	226 (40.6)	
No	47,983 (75.3)	331 (59.4)	

Notes: PD, Parkinson's disease. SMM, somatic multimorbidity. NPM, neuropsychiatric multimorbidity. CMM, cardiometabolic multimorbidity.

Table 1: **Baseline characteristics of included participants.**

hypertension, diabetes, dyslipidaemia, stroke, rheumatoid arthritis or osteoporosis, affective disorders, and dementia, are at higher risk of PD, compared to those without corresponding diseases. Those with (vs. without) multimorbidity, SMM, NPM, and CMM are at around 1.40–2.70 times higher risk of new-onset PD,

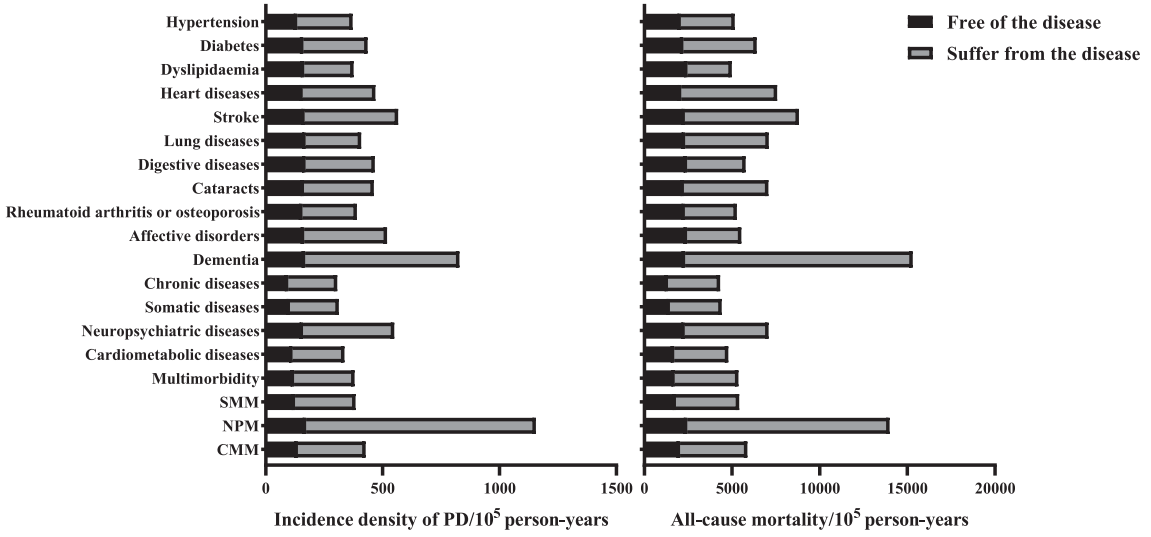

Fig. 1: **Incidence density of PD and all-cause mortality among older adults free of or suffering from chronic diseases or multimorbidity.**
Notes: PD, Parkinson's disease. SMM, somatic multimorbidity. NPM, neuropsychiatric multimorbidity. CMM, cardiometabolic multimorbidity.

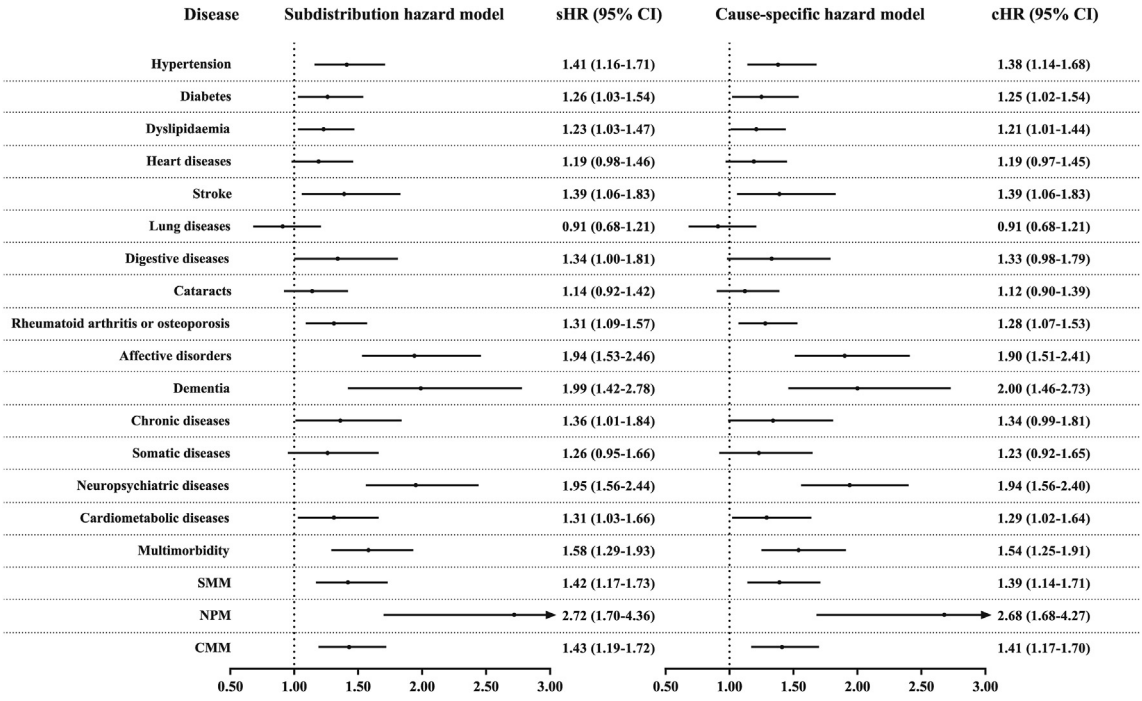

Fig. 2: **Association of chronic diseases and multimorbidity with new-onset PD during a 6-year follow-up**. Notes: sHR, subdistribution hazard ratio. cHR, cause-specific hazard ratio. CI, confidence interval. PD, Parkinson's disease. SMM, somatic multimorbidity. NPM, neuropsychiatric multimorbidity. CMM, cardiometabolic multimorbidity. All models were adjusted for age, sex, residence, education, occupation, household income, marital status, current smoking, current drinking, irregular physical activity, unhealthy diet, abnormal weight, frailty, loneliness, history of cancer, use of psychotropic or sedative medicines, and use of other medicines.

with similar values of sHRs and cHRs. At the same time, participants with NPM and dementia seem to exhibit the highest PD risk. In all the sensitivity analyses, the associations between multimorbidity and new-onset PD remain significant, though the association between certain chronic diseases and new-onset PD vary (Tables S1–S6). However, in the SDoH-stratified analysis shown in Tables S7–S8, we only found significant interactions of household income with neuropsychiatric diseases ($P = 0.027$) and NPM (P for interaction<0.001).

Table S9 confirms that limitations in ADLs, IADLs, and mobility, depressive symptoms, and cognitive impairment are risk factors for PD. Table 2 further indicates that participants with multimorbidity, SMM, NPM, and CMM tend to develop PD-related functional degeneration faster when compared to those without corresponding multimorbidity patterns (all P values < 0.05).

According to Table 3, recent-onset multimorbidity, SMM, NPM, and CMM are significantly associated with increased risks of new-onset PD, with sHRs (95% CIs) of 1.75 (1.23–2.48), 1.45 (1.01–2.06), 3.67 (1.90–7.12), and 1.58 (1.10–2.26) and cHRs (95% CIs) of 1.75 (1.23–2.48), 1.45 (1.02–2.06), 3.72 (1.89–7.31), and 1.58 (1.11–2.25). Although the sHRs and cHRs between prior diagnosed and recent-onset groups appear comparable, and the latter seems more significant, the P values for differences between them are not statistically significant (all >0.05). In addition, only participants with recent-onset diabetes and rheumatoid arthritis or osteoporosis are at significantly higher risks of PD compared to those with prior diagnosed corresponding conditions (P values for difference <0.05).

Tables S10–S14 further indicate that limited recent-onset chronic diseases or multimorbidity patterns can result in faster functional degeneration than prior diagnosed corresponding conditions. We only found that participants with recent-onset affective disorders tended to develop cognitive decline faster and that participants with recent-onset NPM tended to develop IADL limitations and cognitive decline faster when compared to those with prior diagnosed corresponding conditions (P for difference <0.05).

Discussion

In this prospective cohort study, we found positive associations of time-varying chronic diseases and multimorbidity, particularly neuropsychiatric-related, with increased PD risks and faster functional degeneration after considering the competing risk of all-cause death in older adults, which were more pronounced in those

Disease*time	ADL limitations	IADL limitations	Mobility limitations	Depressive symptoms	Cognitive decline
Hypertension					
β	0.022	0.046	0.067	0.014	−0.017
P value	<0.001	<0.001	<0.001	<0.001	<0.001
Diabetes					
β	0.032	0.053	0.086	0.012	−0.021
P value	<0.001	<0.001	<0.001	<0.001	<0.001
Dyslipidaemia					
β	0.012	0.022	0.026	0.004	−0.009
P value	<0.001	<0.001	<0.001	0.024	<0.001
Heart diseases					
β	0.040	0.078	0.067	0.015	−0.025
P value	<0.001	<0.001	<0.001	<0.001	<0.001
Stroke					
β	0.095	0.169	0.147	0.015	−0.030
P value	<0.001	<0.001	<0.001	<0.001	<0.001
Lung diseases					
β	0.035	0.067	0.092	0.009	−0.018
P value	<0.001	<0.001	<0.001	<0.001	<0.001
Digestive diseases					
β	0.020	0.022	0.030	−0.001	−0.011
P value	<0.001	<0.001	<0.001	0.881	0.002
Cataracts					
β	0.029	0.068	0.057	0.011	−0.029
P value	<0.001	<0.001	<0.001	<0.001	<0.001
Rheumatoid arthritis or osteoporosis					
β	0.024	0.041	0.068	0.006	−0.010
P value	<0.001	<0.001	<0.001	0.001	<0.001
Affective disorders					
β	0.041	0.087	0.077	0.006	−0.007
P value	<0.001	<0.001	<0.001	0.112	0.014
Dementia					
β	0.184	0.388	0.205	0.005	−0.050
P value	<0.001	<0.001	<0.001	0.546	<0.001
Chronic diseases					
β	0.031	0.059	0.092	0.024	−0.025
P value	<0.001	<0.001	<0.001	<0.001	<0.001
Somatic diseases					
β	0.028	0.050	0.086	0.021	−0.024
P value	<0.001	<0.001	<0.001	<0.001	<0.001
Neuropsychiatric diseases					
β	0.077	0.177	0.119	0.004	−0.017
P value	<0.001	<0.001	<0.001	0.252	<0.001
Cardiometabolic diseases					
β	0.024	0.049	0.071	0.017	−0.022
P value	<0.001	<0.001	<0.001	<0.001	<0.001
Multimorbidity					
β	0.036	0.070	0.086	0.017	−0.025
P value	<0.001	<0.001	<0.001	<0.001	<0.001
SMM					
β	0.032	0.061	0.083	0.015	−0.024
P value	<0.001	<0.001	<0.001	<0.001	<0.001
NPM					
β	0.160	0.281	0.065	0.066	−0.010
P value	<0.001	<0.001	0.036	<0.001	<0.001

(Table 2 continues on next page)

Disease*time	ADL limitations	IADL limitations	Mobility limitations	Depressive symptoms	Cognitive decline
(Continued from previous page)					
CMM					
β	0.031	0.061	0.070	0.013	−0.023
P value	<0.001	<0.001	<0.001	<0.001	<0.001

Notes: PD, Parkinson's disease. ADL, activities of daily living. IADL, instrumental activities of daily living. SMM, somatic multimorbidity. NPM, neuropsychiatric multimorbidity. CMM, cardiometabolic multimorbidity. All models were adjusted for age, sex, residence, education, occupation, household income, marital status, current smoking, current drinking, irregular physical activity, unhealthy diet, abnormal weight, frailty, loneliness, history of cancer, use of psychotropic or sedative medicines, and use of other medicines.

Table 2: **Association of chronic diseases and multimorbidity with the slope of PD-related functional degeneration during a 6-year follow-up in participants with no PD-related functional impairment.**

with lower household income. Though recent-onset diabetes and rheumatoid arthritis or osteoporosis were more significantly associated with PD than prior diagnosed ones, recent-onset multimorbidity patterns were at comparable risks of PD compared to those diagnosed before. Still, those with recent-onset NPM exhibited faster degeneration in IADLs and cognitive function.

Our findings indicated that chronic diseases and multimorbidity could contribute to an increased risk of new-onset PD and PD-related functional degeneration. Chronic diseases are significantly associated with increased chronic inflammation, which can further contribute to accelerated neurodegeneration and increased risk of PD.[28,29] For instance, systemic inflammation can have a significant impact on the development of neuronal dysfunction caused by specific elements, amyloid, synuclein, and tau.[29] Furthermore, chronic diseases and multimorbidity are commonly associated with increased oxidative stress, which would damage brain cells potentially, including dopaminergic neurons located in the substantia nigra,[30,31] and can further increase the risk of developing PD. The medicines used to treat multimorbidity may also result in increased PD risk. According to prior evidence, beta-antagonists and calcium channel blockers, commonly prescribed for cardiometabolic diseases, can contribute to an increased risk of PD.[32–34] Additionally, certain gastrointestinal prokinetics can lead to drug-induced parkinsonism due to their interference with dopamine receptors and the normal transmission and regulation

Disease	Never	Prior diagnosed	Recent onset	*P* for difference	Never	Prior diagnosed	Recent onset	*P* for difference
	sHR (95% CI)				cHR (95% CI)			
Hypertension	Reference	1.51 (1.16–1.96)	1.94 (1.34–2.81)	0.159	Reference	1.51 (1.16–1.97)	1.94 (1.34–2.81)	0.164
Diabetes	Reference	1.25 (0.95–1.65)	2.14 (1.38–3.33)	0.027	Reference	1.25 (0.95–1.66)	2.15 (1.39–3.34)	0.028
Dyslipidaemia	Reference	1.19 (0.93–1.53)	1.69 (1.20–2.38)	0.062	Reference	1.19 (0.93–1.53)	1.69 (1.20–2.39)	0.061
Heart diseases	Reference	1.18 (0.88–1.56)	1.51 (1.00–2.26)	0.281	Reference	1.18 (0.89–1.56)	1.51 (1.00–2.27)	0.287
Stroke	Reference	1.16 (0.76–1.77)	1.27 (0.66–2.43)	0.808	Reference	1.16 (0.76–1.76)	1.28 (0.65–2.49)	0.806
Lung diseases	Reference	1.11 (0.76–1.62)	0.62 (0.28–1.40)	0.495	Reference	1.11 (0.76–1.63)	0.62 (0.28–1.40)	0.493
Digestive diseases	Reference	1.41 (0.92–2.17)	0.76 (0.31–1.84)	0.624	Reference	1.41 (0.92–2.17)	0.76 (0.31–1.84)	0.621
Cataracts	Reference	1.00 (0.71–1.39)	1.47 (0.99–2.18)	0.167	Reference	1.00 (0.72–1.39)	1.47 (0.99–2.18)	0.166
Rheumatoid arthritis or osteoporosis	Reference	1.33 (1.03–1.72)	1.95 (1.43–2.66)	0.026	Reference	1.33 (1.03–1.71)	1.95 (1.42–2.67)	0.025
Affective disorders	Reference	1.70 (1.18–2.46)	1.86 (1.17–2.95)	0.755	Reference	1.70 (1.17–2.48)	1.86 (1.18–2.95)	0.756
Dementia	Reference	1.49 (0.77–2.90)	2.80 (1.69–4.62)	0.107	Reference	1.50 (0.84–2.69)	2.82 (1.71–4.65)	0.090
Chronic diseases	Reference	1.61 (1.07–2.42)	1.73 (1.01–2.96)	0.743	Reference	1.61 (1.05–2.47)	1.73 (1.01–2.95)	0.754
Somatic diseases	Reference	1.61 (1.10–2.37)	1.83 (1.10–3.05)	0.551	Reference	1.61 (1.07–2.45)	1.83 (1.09–3.06)	0.563
Neuropsychiatric diseases	Reference	1.76 (1.24–2.49)	2.02 (1.35–3.02)	0.573	Reference	1.76 (1.26–2.47)	2.02 (1.36–3.00)	0.572
Cardiometabolic diseases	Reference	1.37 (0.99–1.89)	1.53 (0.97–2.41)	0.576	Reference	1.37 (0.98–1.90)	1.53 (0.98–2.39)	0.588
Multimorbidity	Reference	1.57 (1.19–2.08)	1.75 (1.23–2.48)	0.497	Reference	1.57 (1.18–2.10)	1.75 (1.23–2.48)	0.506
SMM	Reference	1.38 (1.05–1.81)	1.45 (1.01–2.06)	0.761	Reference	1.38 (1.05–1.81)	1.45 (1.02–2.06)	0.769
NPM	Reference	1.06 (0.24–4.64)	3.67 (1.90–7.12)	0.124	Reference	1.07 (0.26–4.41)	3.72 (1.89–7.31)	0.113
CMM	Reference	1.60 (1.24–2.07)	1.58 (1.10–2.26)	0.944	Reference	1.60 (1.24–2.06)	1.58 (1.11–2.25)	0.937

Notes: sHR, subdistribution hazard ratio. cHR, cause-specific hazard ratio. CI, confidence interval. PD, Parkinson's disease. SMM, somatic multimorbidity. NPM, neuropsychiatric multimorbidity. CMM, cardiometabolic multimorbidity. All models were adjusted for age, sex, residence, education, household income, marital status, current smoking, current drinking, normal weight, physical activity, and healthy diet. *P* for difference was false discovery rate-adjusted.

Table 3: **Association of prior diagnosed and recent onset chronic diseases and multimorbidity from 2013 to 2015 with new-onset PD from 2015 to 2019.**

of dopamine.[35] Some analgesics, such as aspirin and acetaminophen, may also increase the risk of PD if overdosed.[36–38] Finally, exposure to certain oral antibiotics, e.g., macrolides used for respiratory infections, is positively associated with an elevated risk of PD.[39] Therefore, the simultaneous administration of multiple medications in patients with multimorbidity can result in the accumulation of adverse effects, leading to a significant elevation in the risk of developing PD.

Of all chronic diseases included, neuropsychiatric diseases, e.g., dementia, were associated with PD and PD-related functional degeneration most. Prior evidence suggests that there are some overlaps between the pathological mechanisms of dementia and PD.[40] Cognitive impairment is acknowledged to occur throughout PD, from early to more advanced stages.[41] The shared pathological mechanisms of dementia and PD, such as increased chronic inflammation and oxidative stress mentioned before, can help interpret our findings.[29,31] Additionally, patients with dementia often encounter changes in neural plasticity, including adjustments in synapse plasticity and alterations in neurotransmitter signalling, which can potentially contribute to an elevated risk of new-onset PD.[42] The increased PD risk associated with dementia can also be attributed to the side effects of the medicine used to treat dementia-related psychiatric disorders. For instance, the use of antipsychotics is associated with a significantly increased risk of new-onset PD according to prior evidence.[43,44]

It is worth highlighting participants who developed chronic diseases recently faced comparable or even higher risks of new-onset PD compared to those with previously diagnosed corresponding conditions. One possible explanation is that individuals with prior diagnosed multimorbidity may have changed their unhealthy lifestyles, developed better health management, and followed medical advice, thereby resulting in a similar or even lower PD risk compared to those with acute-onset chronic diseases. Furthermore, participants experiencing new-onset chronic diseases like diabetes and arthritis may be amid disease progression characterised by elevated levels of acute inflammation and oxidative stress, significantly increasing the risk of developing PD. Older adults with emerging chronic diseases may also seek medical attention only when they start feeling unwell, where their conditions are relatively severe, and thus lead to a higher cumulative risk of PD. In addition, new-onset chronic diseases and morbidity in old age may signal rapid physical frailty, as well as excess accumulation of common risk factors for chronic diseases and PD. Finally, those highly susceptible to PD due to severe chronic diseases may have already developed PD before and were excluded at baseline, leaving behind those with better disease control and lower risk of PD. Also, our study revealed that individuals with recent-onset NPM experienced faster deterioration in IADL limitations and cognitive decline vs. those previously diagnosed, emphasizing its critical role as a risk factor for PD.

Key prevention populations for mitigating the PD risk attributed to NPM, namely, those with lower household income, were identified by our research. Older adults who are poor may adopt unhealthy lifestyles and encounter increased health risks and barriers to accessing healthcare, such as inadequate medical resources and increased healthcare inequalities, which can lead to delayed diagnosis and management of chronic diseases, further amplifying the risk of progression to PD.[45,46] Despite the non-significant statistical interaction, our findings implied the importance of preventing PD risk in single older adults. They are at higher risk of social isolation, psychological stress, and a lack of social support and communication, which can contribute to neurological disorders and heightened inflammatory responses, thereby increasing the risk of PD.[29,47] Additionally, single older are at higher risk of adopting unhealthy lifestyles, which may further contribute to an increased risk of developing PD.[48]

This study holds significant importance in both public health and clinical practice. Our findings underscore the necessity of early detection, timely treatment, and effective management of chronic diseases and multimorbidity in the prevention of PD, especially among lower-income populations. For older adults who present with new-onset neuropsychiatric diseases or NPM, it is crucial to monitor and prevent functional impairment and cognitive decline, facilitating early screening and prevention of PD. However, when it comes to those with new-onset somatic conditions, monitoring ADLs, IADLs, mobility, depressive symptoms, and cognitive function alone may not capture the risk of PD accurately. Instead, a more diverse set of markers for PD risk identification is needed.

To our knowledge, this is the first and most comprehensive population-based cohort study to investigate the associations of chronic diseases, multimorbidity patterns, and their recent onset with new-onset PD and PD-related functional degeneration. The time-dependent analysis used in this study helps capture the time-varying chronic conditions of older adults more accurately. The competing-risk analyses based on subdistribution and cause-specific hazard models and mixed-effect models with random intercepts and slopes used in this study ensure the precision of our research methodology. A set of sensitivity analyses were also conducted to ensure the robustness of our conclusions. Furthermore, potential effect modifications of SDoH were explored to help policymakers identify key intervention populations for PD risk attributed to chronic disease and multimorbidity. The large sample size from diverse European countries and the excellent population

representation of SHARE strengthen the reliability and generalizability of our findings.

Our study is subject to several limitations. The major limitation of this study is that the assessment of chronic diseases and PD relied on self-reported physician diagnoses or treatments provided by the participants, which may introduce misclassification bias. Although we have performed a series of sensitivity analyses to confirm our conclusions, this bias cannot be eliminated. Brain imaging examinations of patients can help correctly diagnose PD, but the relevant information is not available in SHARE. In addition, this study is an observational study based on cohort data, and the causal associations cannot be inferred, which needs to be further verified in future. Finally, some confounding factors, such as blood biomarkers, were not adjusted due to the data limitations, which may influence our conclusions.

In this prospective cohort study based on older European adults from SHARE, our study found significant positive associations of time-varying chronic diseases, multimorbidity, and their recent onset with subsequent risks of PD and related functional degeneration, especially among lower-income older adults. Policymakers should promote early PD screening in older adults with recent-onset chronic diseases and multimorbidity, especially those neuropsychiatric-related, to minimise the risk and burden of PD.

Contributors

JL and ZR conceptualised and designed the study. ZR and YX managed, analysed and verified the data. ZR and YX prepared the first draft. ZR, YX and JL interpreted the data, and JL, JS, LA, and YH were responsible for editing and proofreading the manuscript. All authors contributed to the critical revision of the manuscript and read and approved the final version of the manuscript. All authors had full access to all the data in the study and accepted responsibility for the decision to submit for publication.

Data sharing statement

Data for the study came from the SHARE project and are available to all researchers for purely scientific purposes upon request on the SHARE website (http://www.share-project.org/).

Declaration of interests

The authors declare no conflict of interest regarding this manuscript.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.102265.

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