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"The Regional Burden of Parkinson's Disease in Kazakhstan 2014–2021: Insights from National Health Data"

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by

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ABSTRACT

Background. Globally, neurological illnesses are the primary cause of disability, with Parkinson's disease (PD) showing the greatest rate of growth. The Global Burden of Disease (GBD) study evaluated 5.5 million Disability-adjusted life-years (DALYs) in 2017. The GBD study underscores the need for research in regions lacking data, such as Central Asia (CA).

Methods. Using the Unified National Electronic Health System of Kazakhstan over eight-year span (2014-2021), we explored the epidemiology, DALYs, and all-cause mortality in the PD cohort. Cox proportional hazards regression models and Kaplan-Meier analysis with sensitivity analyses were performed to evaluate the sociodemographic, hypertension and Charlson Comorbidity Index (CCI) affecting survival.

Results. The total cohort comprised 10,125 patients, with a significant increase in the prevalence from 4.2 in 2014 to 44.1 in 2021. While mortality rates varied, the eldest (≥80) and youngest (<50) age groups had the highest (137.05) and lowest (16.40) rates per 1000 person-years, respectively. Over the course of observation, 29,474 DALYs were lost due to PD, with a substantial contribution of years of life lost. Finally, there was an increased risk of all-cause mortality among the male sex (adjusted hazard ratio (aHR) 1.6; 1.5-1.8), older age (1.02; 1.01-1.03), greater CCIs and Kazakh ethnicity. Interestingly, patients with comorbid hypertension had higher probability to survive (0.63; 0.57-0.70).

Conclusion. To our knowledge, this is the first study in CA to explore the burden of PD. The increasing burden of PD among males and ethnic Kazakhs underscores the necessity for focused interventions. Further efforts must be made to understand the inverse association of hypertension in PD cohort.

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INTRODUCTION

Parkinson’s disease (PD) is one of the most common progressive neurodegenerative disorders, affecting elderly people. It is among the conditions that are growing the fastest in the world, and has a significant impact on disability (Bloem, Okun, & Klein, 2021; Poewe et al., 2017). Lewy bodies and the loss of dopaminergic neurons in the midbrain's substantia nigra are distinctive pathological features of PD (Bloem et al., 2021; Reich & Savitt, 2019). The International Parkinson and Movement Disorder Society (MDS) defines the core feature of PD as motor Parkinsonism is defined by rigidity or rest tremor in addition to bradykinesia (Postuma et al., 2015). To date, age is the most influential risk factor for PD, with potential associations with various air pollutants ("Global, regional, and national burden of Parkinson's disease, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016," 2018). Although clinical PD diagnosis characterized by bradykinesia and key motor features, molecular pathogenesis involves diverse pathways, suggesting multiple triggering mechanisms contributing to PD development (Outeiro et al., 2023; Poewe et al., 2017).

PD is a chronic, non-fatal condition whose frequency is rising due to an aging population. Global disability and mortality indices for PD have rapidly risen, doubling in prevalence over the past 25 years ("Parkinson disease," 2023). Today, the most common causes of disability globally are neurological illnesses, and PD is the one among them that is most increasing. Depending on estimates from the Global Burden of Disease (GBD) study ("Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017," 2018), in 2017, the reported prevalence of PD was 8.5 million (95% CI 7.0-10.1), with an incidence of more than 1.0 million (95% CI 0.85-1.2). The most recent GBD study (Deuschl et al., 2020) evaluated 5.5 million Disability-adjusted life-years (DALYs) and 1.2 million years lived

with disability (YLDs) for PD. The number of patients with PD is expected to growth as population life expectancy rising, causing the number of patients with advanced PD to increase. To address this burden, there is a need for better preventive strategies and effective treatments for PD. More studies on incidence and prevalence are essential, especially in areas where data are not available, to analyze temporal trends and their driving factors ("Global, regional, and national burden of Parkinson's disease, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016," 2018).

There is lack of comprehensive research on the epidemiological burden of Parkinson's disease (PD) in Eurasian countries. Although there is an abundance of data available regarding disease burden in high-income countries, there is a lack of comprehensive data from developing countries, especially from Central Asia. This research sought to evaluate the burden of PD in the Republic of Kazakhstan, the largest country within Central Asia.

METHODS

Study Design and Population.

This study collated extensive administrative health data from the Unified National Electronic Health System (UNEHS) spanning over a period of 2014 to 2021. The UNEHS was initiated in 2003, was implemented in 2014, and provided access to health claims from multiple data sources, such as inpatient-outpatient electronic health registries, registries of dispensaries, and many others, which are implemented throughout the country. Further clarification on the database and methodology is available in preceding study (Gusmanov et al., 2023). The International Classification of Diseases (ICD) was utilized to identify individual PD occurrences. Raw records were taken out from the database of the "G20" ICD code from the outpatient dispensary registry. The cases were confirmed using conventional protocols based on the local and MDS norms,

including physical examination, magnetic resonance imaging, transcranial ultrasound dopplerography and UK Parkinson's Disease Society Brain Bank criteria ("Clinical protocols of the Ministry of Health of the Republic of Kazakhstan: Parkinson's Disease," 2016; Postuma et al., 2015). 15,898 patient records made up the original set of data. Thorough data cleaning resulted in 10,125 records (Figure S1), each of which had unique population registry number (RPN ID). The population size of Kazakhstan and the rate of growth were obtained from the local Bureau of National Statistics ("Demographic statistics," 2023).

Exposure and Covariates.

Individual patient data encompassed essential demographic information, such as birthdate, sex, ethnicity, residency, ICD-10th code for diagnosis, PD diagnosis dates, and death date with the corresponding cause if applicable. The study entry was January 1, 2014, and the endpoint of the follow-up period was June 30, 2021. Using the dispensary registry, we were able to determine the date of each individual RPN ID's diagnosis. Age of disease diagnosis was determined using the difference of diagnosis and birth dates, and subsequently, this variable was stratified into five categories: <50 years of old, 50-59, 60-69, 70-79, and individuals aged 80 and above. Since more than 50 ethnicities were present, we grouped them into three ethnicities: Kazakhs, Russians, and Others. The data for the ethnicity covariate were missing from 91 (0.90%) observations. Considering their low prevalence, they were recoded into the “Other” group.

Outcome Assessment

Crude incidence rate as well as prevalence rates were determined by division of newly diagnosed and prevalent cases by the number of people at the end of each consecutive year. For age-specific incidence and prevalence, these numbers were divided by the cohort size in the corresponding age groups and reported with a population multiplier. The prevalence analysis had been calculated

cumulatively and the participant was excluded from the analysis only in case of death. Time at risk was approximated as the difference in study entry date, and either death or the end of the follow-up date, whichever came first. CCIs used a four level scale with an additional adjustment on age. Specifically, with each decade following the age of 50 at diagnosis, we have increased the overall score by one point. YLLs were evaluated as multiplication of the death counts in each age groups by the corresponding remaining lifespan, extracted from the life table ("Global, regional, and national age-sex specific mortality for 264 causes of death, 1980-2016: a systematic analysis for the Global Burden of Disease Study 2016," 2017). Regarding the YLDs, a prevalence-based approach was used, where index was multiplied by the disability weight (DW). The DW varied for the severity levels of PD (e.g. mild, moderate and severe). Since the severity was not available in the UNEHS, the average of three DWs was taken ("WHO methods and data sources for global burden of disease estimates 2000-2019," 2020). The total of YLLs and YLDs was then used to compute DALYs.

Statistical analysis and methods.

Incidence and prevalence rates are expressed per 100,000 people in each age category. The death rate was given in 1000 person-years. STATA V.18 was used for data management, cleaning, and formal analysis. A PD prevalence map has been constructed using QGIS 3.32.1. For categorical variables, data were reported as percentages; for values with a normal distribution, as mean and standard deviation (SD); and for asymmetric distributions, as median and interquartile range (IQR). We performed exploratory, predictive data analysis, and to determine the crude and adjusted hazard ratios, Cox proportional hazards regression analysis was used. The Kaplan-Meier survival analysis was made with log-rank test and variations in survival estimations for age, sex, comorbidity, CCIs, and ethnicity with all-cause mortality were determined relying on the Wald's

test. To verify the credibility of the survival estimates a number of sensitivity analysis were performed. Two-sided P values were considered statistically significant when they were less than 0.05. Considering that the study is retrospective in nature, the Nazarbayev University Institutional Review Ethics Committee accepted this study (NU-IREC 490/18112021) and waived the requirement for informed consent. The "STrengthening the Reporting of OBservational studies in Epidemiology" (von Elm et al., 2008) principles were followed in conducting the study. The corresponding author can provide the data supporting the study's conclusions upon request. Because of ethical and privacy concerns, the data are not publicly accessible.

RESULTS

Socio-Demographic Characteristics

Table 1 provides a summary of the patients' sociodemographic characteristics. During the study period, diagnosis was observed more in females (60.7%) than males (39.3%). The majority of patients was between the ages of 60 and 69 years (35.5%), with the percentage being the lowest among those who were 50 years of age and younger (6.2%). An average age for PD diagnosis was 66.9 years (10.7), while the length of the disease was 2.5 years (IQR 1.3-4.2) at median. Among the study cohort, Kazakhs made up more than half of the population with PD (50.9%), followed by Russians (30.8%) and "other" ethnicities (18.3%). Co-existing hypertension was present in 57.9% patients with PD.

Table 1. Social, medical, and demographic characteristics of patients.

	Total (n=10,125)	**Female (6,142; 60.66%)**	**Male (n=3,983; 39.34%)**	**p-value**
Socio-Demographics				
Age category, n (%)				<0.001

<50 y.o.	625	337 (5.49%)	288 (7.23%)	
50 - 59 y.o.	1,807	977 (15.91%)	830 (20.84%)	
60 - 69 y.o.	3,591	2,143 (34.89%)	1,448 (36.35%)	
70 – 79 y.o.	3,141	2,041 (33.23%)	1,100 (27.62%)	
≥80 y.o.	961 (9.49%)	644 (10.49%)	317 (7.96%)	
Ethnicity, n (%)				<0.001
Kazakh	5,157	2,958 (48.16%)	2,199 (55.21%)	
Russian	3,119	2,069 (33.69%)	1,050 (26.36%)	
Other	1,849	1,115 (18.15%)	734 (18.43%)	
Outcome				<0.001
Living	8,384	5,260 (85.64%)	3,124 (78.43%)	
Died	1,741	882 (14.36%)	859 (21.57%)	
Charlson comorbidity index (CCI)				<0.001
0	420	212 (3.45%)	208 (5.22)	
1-2	3,810	2,205 (35.90%)	1,605 (40.30%)	
3-4	4,515	2,846 (46.34%)	1,669 (41.90%)	
≥5	1,380	879 (14.31%)	501 (12.58%)	
Comorbidity				
Hypertension, n (%)				<0.001
Yes	5,862	3,824 (65.23%)	2,038 (34.77%)	

Epidemiological and mortality estimates

The incidence rate increased slightly within the observation period, especially for those aged 80 years and above, increasing to 56% by 2021 (Figure S2). However, the prevalence estimates have grown substantially. In particular, from 4.2 in 2014 to 44.1 in 2021 per 100,000 (Figure S2). In terms of age-specific prevalence, the lowest and highest rates were observed in the youngest and the eldest groups, respectively. Concerning the mortality analysis, the death rate in the whole PD

cohort was 60.4 (95% CI 57.6-63.3) per 1000 person-years, with the highest rate for those aged 80 years, and gradually decreasing for each consecutive age group.

In Kaplan-Meier survival analysis, the chance to survive was reported to be greater in female patients in contrast to males, CCI=0 and in Kazakh ethnicity relative to others including Russian ethnicity (Figure 1, Table 2) and CCIs=1-2, CCIs=3-4 and CCIs ≥5. Patients with comorbid hypertension had higher chances to survive. Finally, the results indicated an elevation of all-cause mortality risks among the male sex (aHR) 1.62 (95%CI 1.47-1.78), greater age (aHR 1.02; 95%CI 1.01-1.03); CCI=1-2 (aHR 2.89; 1.64-5.11), CCI=3-4 (aHR 6.23; 3.47-11.20), and CCI≥5 (aHR 8.02; 4.41-14.60), however, hypertensive patients (aHR 0.63; 0.57-0.70), Russian (aHR 0.87; 95%CI 0.78-0.97) and other (aHR 0.99; 95%CI 0.87-1.12) ethnicities showed a lower risk when compared to female sex, younger age, CCI=0, Kazakh ethnicity and normotensive patients (Table 2).

Figure 1. Survival probability by sex, ethnicity, CCI and hypertension

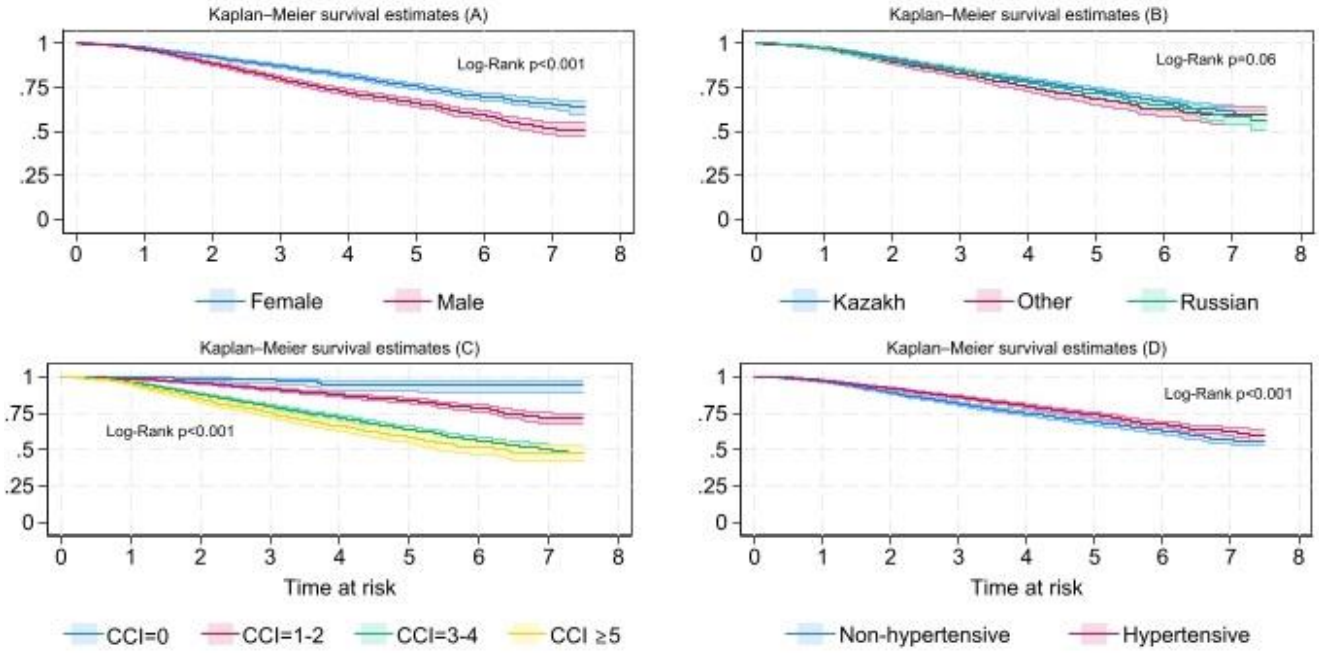


Table 2. Factors associated with overall mortality in PD patients.

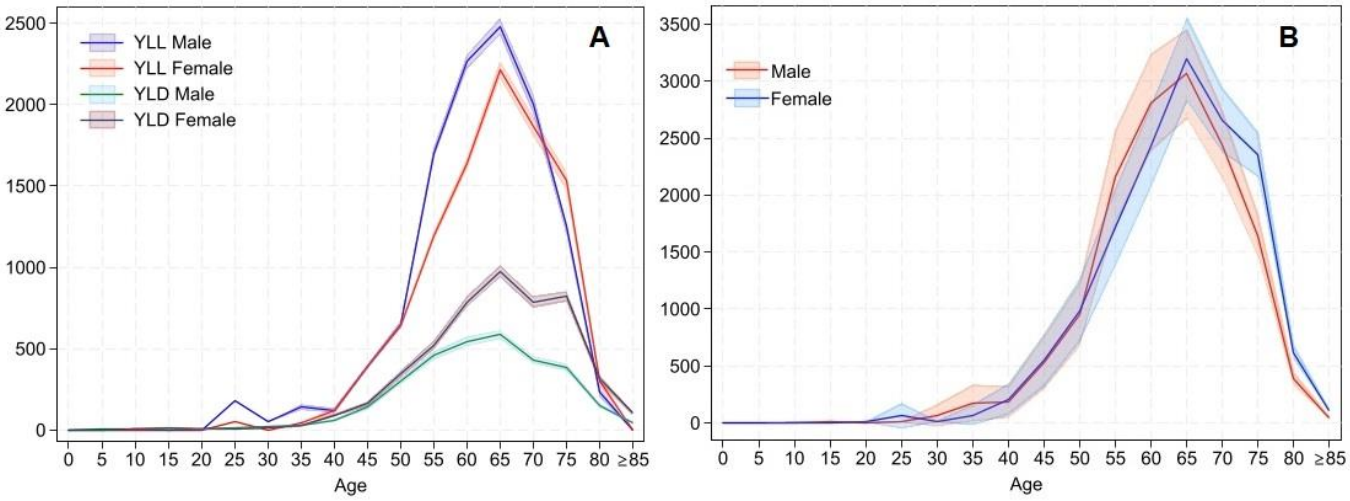
Variables	Model 1. Unadjusted HR and 95% CI	p-value	Model 2. Adjusted HR and 95% CI	p-value
Sex				
Female	1.0		1.0	
Male	1.52 (1.38-1.67)	<0.001	1.62 (1.47-1.78)	<0.001
Age	1.04 (1.03-1.05)	<0.001	1.02 (1.01-1.03)	<0.001
Ethnicity				
Kazakh	1.0		1.0	
Russian	1.07 (0.96-1.19)	0.20	0.87 (0.78-0.98)	0.02
Other	1.16 (1.02-1.31)	0.02	0.99 (0.87-1.12)	0.89
CCI				
0	1.0		1.0	
1-2	3.71 (2.13-6.45)	<0.001	2.89 (1.64-5.11)	<0.001
3-4	9.10 (5.26-15.72)	<0.001	6.23 (3.50-11.20)	<0.001
≥5	11.10 (6.36-19.24)	<0.001	8.02 (4.41-14.60)	<0.001
Hypertension				
No	1.0		1.0	
Yes	0.79 (0.72-0.87)	<0.001	0.63 (0.56-0.69)	<0.001

HR – Hazard Ratio; Model 1 unadjusted; Model 2 adjusted for sex, age, ethnicity, CCI and hypertension.

Disability-adjusted life years

Age- and sex-adjusted YLLs, YLDs, and DALYs in the PD cohort are presented in Figure 2 (Table S3). Throughout the study period, 29,474 DALYs were lost to follow-up due to PD. The YLL and YLD values were 21,287 and 8,187, respectively. The highest contribution of both premature deaths and years lost due to disability to DALY is observed at the ages of 65-75 years when YLLs and YLDs are the highest. The total DALYs for men and women were similar (14, 491 and 14, 982, respectively).

Figure 2. Sex-adjusted YLLs, YLDs (A) and DALYs (B)



Sensitivity analysis

PD was uncommon in patients aged 50 years and less. Consequently, in the sensitivity analysis for the survival we excluded participants falling in this age group (Figure S4 (A)), and the estimates (aHR) remained unchanged. Similarly, further exclusion of individuals aged over 80 years at the time of study entry did not result in alterations to the estimates (Figure S4 (A)). The exclusion of age-adjustment from the CCI scores showed increase in estimates solely for CCIs; however, considering the importance of diagnosis age we decided to proceed with full (adjusted) model. A propensity-score matching was performed using age, sex, CCI and ethnicity as covariates, to test the effect of hypertension on survival in 3,690 hypertensive versus 3,690 non-hypertensive patients (Figure S5). The estimates remained unchanged (log-rank $p<0.001$). Finally, the study findings suggest that COVID-19 did not have a significant impact on survival within the study cohort. The substantially overlapping confidence intervals for the mortality rate indicate a substantial degree of uncertainty; however, the consistency across estimates suggests robustness in our survival estimates (Figure S4 (B)).

DISCUSSIONS

Neurological disorders are currently the primary cause of disability worldwide, with PD being the most rapidly growing disorder. To our knowledge, it is the pilot study from Kazakhstan to evaluate the burden of PD depending on the large-scale outpatient dispensary registry. In the cohort, females accounted for 60%, the majority were Kazakhs, and those aged 60-69. Hypertension was a comorbiding in over half of the individuals, and it is appeared to be paradoxically associated with survival. Despite the fact that the incidence rate rose during the observation period, there was a minor decrease in 2020. In spite of the female predominance, males contributed more significantly to the disability-adjusted life years.

Epidemiological and mortality estimates

Despite an increase in the incidence estimates during the observation period, there was a slight decrease in 2020. The estimates has appeared to be slightly affected by the Covid-19 lockdown. Although the lowest index across the study period was in April 2020, a month after the declaration of stringent lockdown (Yergaliyeva, 2020), it had begun to rise, and by the November of 2020 it reached the highest mark. Overall, the findings demonstrate an increase in PD incidence, prevalence, and mortality over the 8 years, which is aligned with worldwide trends (Deuschl et al., 2020; "Global, regional, and national burden of Parkinson's disease, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016," 2018; Lampropoulos, Malli, Sinani, Gourgoulianis, & Xiromerisiou, 2022). Our study showed that PD prevalence was substantially lower than global estimates ("Global, regional, and national burden of Parkinson's disease, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016," 2018), but similar to the regional estimates (Ou et al., 2021). However, unlike our approach, the study used ICD-10 codes G21 (secondary Parkinsonism) and G22 (Parkinsonism in diseases classified elsewhere) in

addition to G20 (Parkinson's disease). Nevertheless, our estimates are significantly lower than those for neighboring Russia (Rozhdestvensky, Delov, Marks, Gaponenko, & Khanokh, 2020), former USSR members Estonia (Taba & Asser, 2002) and Azerbaijan (Aliyeva, 2021). Of particular note is these studies did not provide details regarding the employed ICD-10th codes, for this reason, discrepancies might be explained by case identification. On the other hand, an epidemiological study from Ukraine (Trufanov, Machado de Oliveira, Svyrydova, & Suchowersky, 2023) which employed only “G20”, reported estimates that were aligned with our indices. A previous review (Kaiyrzhanov et al., 2019) that utilized data from a doctoral thesis showed that the prevalence of PD is 65 per 100,000 individuals in Kazakhstan. However, the reference was not available, and we failed to reach its methodological approaches. Furthermore, the validity of PD diagnosis is still unsatisfactory (Rizzo et al., 2016). Accuracy has not significantly improved in recent decades, particularly in the early stages of the disease. These results imply that a large fraction of the patients might be misdiagnosed and/or unregistered. However, the increasing trends across the period are in line with world estimates (Deuschl et al., 2020; Lampropoulos et al., 2022). This can be partially explained by the increasing lifespan, which may lead to an increase in the prevalence of PD. Interestingly, both the incidence and prevalence of PD were less common in males than in females, while global estimates have reported inverse predominance (Abbas, Xu, & Tan, 2018; "Global, regional, and national burden of Parkinson's disease, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016," 2018). The reasons for these are likely multifactorial, which can be explained by variations in access to healthcare or differences in healthcare-seeking behavior, underdiagnosis/misdiagnosis due to differences in symptom presentation or healthcare utilization. Furthermore, environmental exposures could also contribute to variations. For instance, smoking has a protective effect against

PD (Allam, Campbell, Hofman, Del Castillo, & Fernández-Crehuet Navajas, 2004; Mappin-Kasirer et al., 2020). According to the Global Adult Tobacco Survey in Kazakhstan ("Global Adult Tobacco Survey in Kazakhstan, 2019," 2019), the prevalence of smoking among men is six times greater than that among women. However, in European countries, the ratio of smokers between sexes (*Smoking among adults*, 2021) and sex-adjusted PD prevalence differs conversely (Brakedal, Toker, Haugarvoll, & Tzoulis, 2022; Fall et al., 1996). To further understand these associations, it is crucial that studies concentrate on this matter.

The north, eastern, and central parts had the greatest prevalence of PD; however, the nearby administrative units showed lower indices (Figure S6). It is worth noting that it is expressed as per 100,000, and due to the absence of data on age distributions, the geographical prevalence estimates may not accurately reflect the variations between regions. Further studies should try to explore the age-specific prevalence estimates.

According to the findings of this study, more than half of the participants were diagnosed with hypertension. Furthermore, its role in survival was “protective” which is raising some concerns in regard to estimates’ credibility. Thus, hypertension was associated with a lower risk of death, despite its prevalence in the study was higher than in general population of Kazakhstan (Yerdessov et al., 2022), but similar to those reported in the PD cohort (Minar, Dragasek, & Valkovic, 2022; Tulbă et al., 2021). The nature of hypertension in autonomic failure is explored yet. Injury to the end organ linked to plasma renin activity that only manifests itself after chronic, untreated essential hypertension. Consequently, the decreased renin level that in autonomic failure reported to have a protective effect against hypertension complications (Pathak & Senard, 2006). In addition, use of calcium channel blockers in PD patients was associated with reduced risk of death (Pasternak et al., 2012). Nevertheless, the reduction may be explained by confounding factors that were not

taken into account, or by presence of complex syndrome that cause of this paradoxical association, which need to be thoroughly explored. These findings might substantially affect the reliability of the data, which is not concordant with the literature (Tvete & Klemp, 2022). Nevertheless, our mortality rates are within the range reported in the previous studies (Okunoye, Horsfall, Marston, Walters, & Schrag, 2021; Ryu, Han, & Cho, 2023).

Disability-adjusted life years

The 2016 Global Burden of Disease study reported the level of standardized YLL rates for each cause and the trend since 2006, represented as the annualized rate of change in the age-standardized YLL rate. PD has been one of the two causes of significantly positive rates of change since 2006 ("Global, regional, and national age-sex specific mortality for 264 causes of death, 1980-2016: a systematic analysis for the Global Burden of Disease Study 2016," 2017). The findings of our study are concordant with the literature, and the contributions of YLLs to DALY and DALYs for females were higher ("Global, regional, and national burden of Parkinson's disease, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016," 2018). However, unlike global trends (Ou et al., 2021), our YLD estimates were conversely oriented, with female patients having a higher burden. This might be related to the higher prevalence in females in our study; however, YLLs were less due to increased mortality in males. The distribution of DALYs among the regions showed a specific pattern that developed concurrently with prevalence rates.

Sensitivity analysis

Based on the sensitivity analysis, our results demonstrated the reliability of survival estimates. Its consistency, even after excluding specific age groups and testing the age-adjustment effects of covariate stayed unchanged. These results confirm the resilience of our conclusions regarding the impact of COVID-19 on survival within the study cohort.

Strengths and Limitations

Our findings are important for several reasons, as follows. To begin with, this is the first study from Central Asia using national healthcare database to illustrate the burden of PD. The loss of disability-adjusted life years in the region has not been thoroughly studied. Given that other Central Asian nations share a common culture, lifestyle, and healthcare system, it is possible to extrapolate the results of our study to these nations. Furthermore, this study shows that the occurrence of PD has varied geographically. This information may influence policymakers and lead to modifications in health-related regulations. However, our study has a few limitations. Firstly, the assessment of disease epidemiology is based exclusively on secondary data, which may not encompass all the PD cases. Important risk factors like genetics, environmental factors, brain trauma, and the existence of Lewy bodies are not comprised in this database. Moreover, an approximation of the disability weight was made for each severity level in DALYs estimation. The lack of information on pain severity prevents us from making a more accurate calculation.

CONCLUSIONS

To the best of our knowledge, this is the first Central Asian study designed to explore the burden of PD based on large-scale outpatient dispensary registry. This resulted in a substantially greater percentage of females in the PD population, highlighting the significant burden of PD in males and those aged 60 and above. This research highlights how administrative data can help shape policy and health system reactions to PD. Furthermore, the effect of hypertension on autonomic failure should be evaluated in future research. Despite its limitations, this study is expected to contribute valuable knowledge to future research in developing countries.

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APPENDICES

Figure S1. Flow chart of the cohort selection process from the UNEHS.

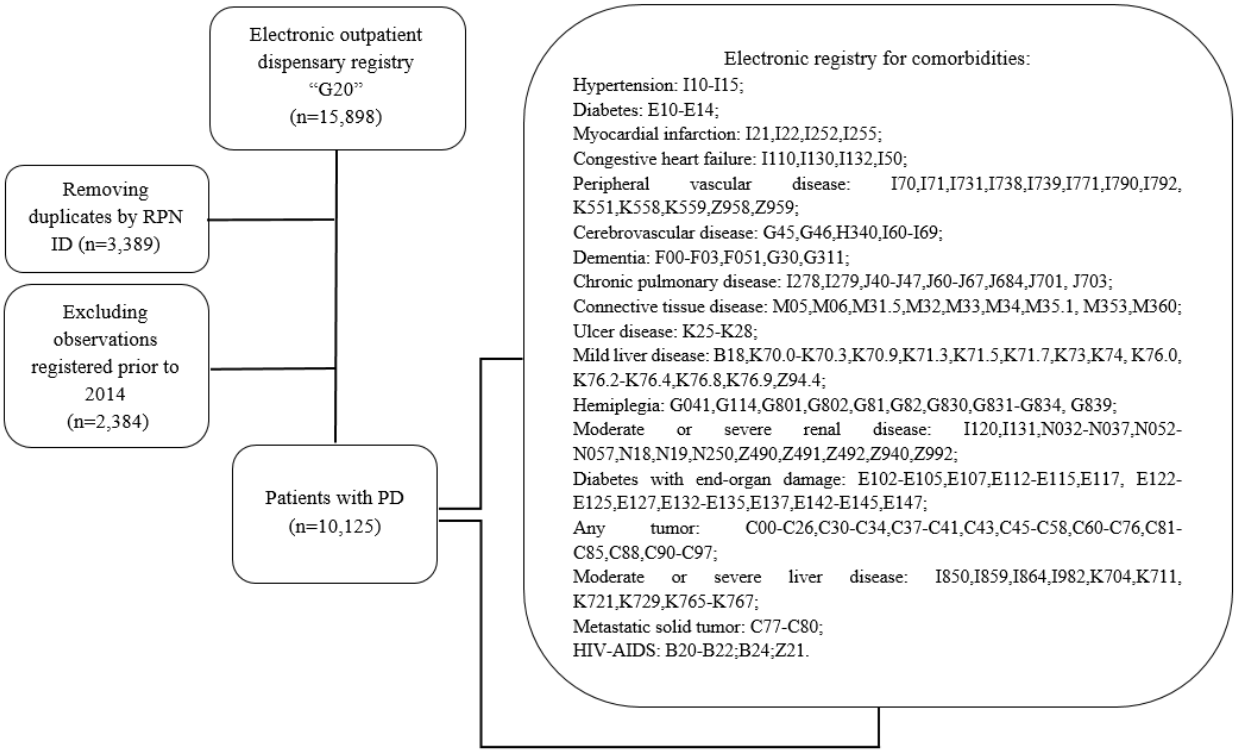


Figure S2. Crude and age-specific incidence and prevalence of Parkinson's disease (per 100,000).

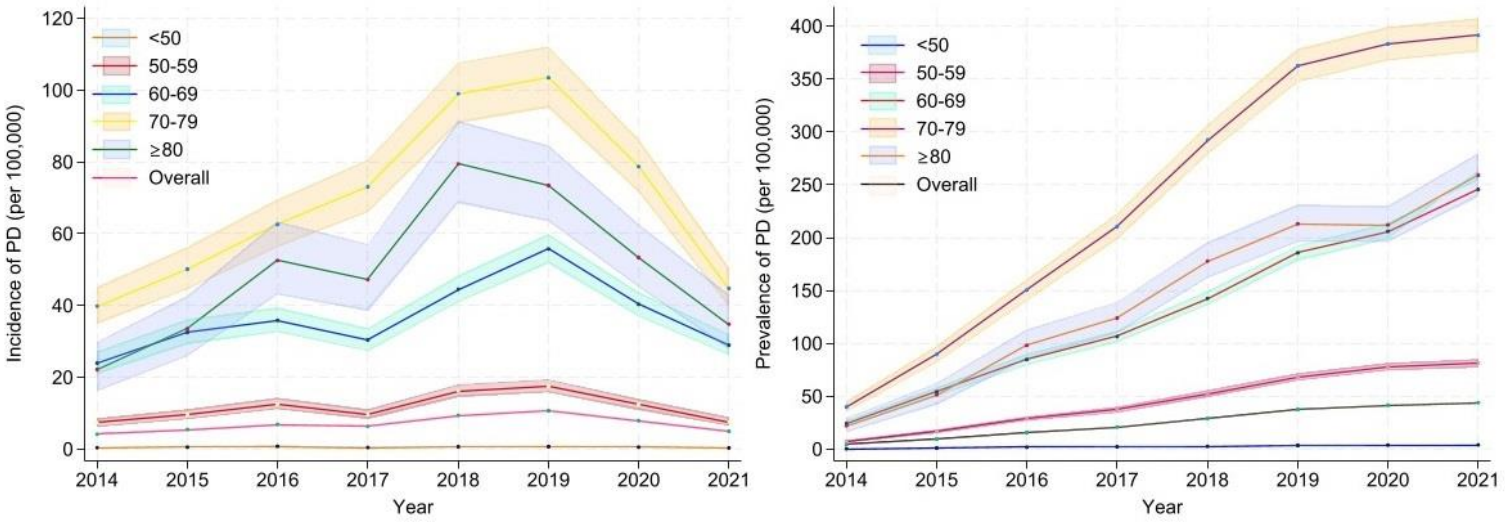


Table S3. Years of life lost due to premature death (YLL) and years lived with disability (YLD), and disability-adjusted life years (DALY) for PD adjusted on age and sex.

Age-group	Life expectancy	Female			Male			Total		
		YLL	YLD	DALY	YLL	YLD	DALY	YLL	YLD	DALY
≤5	84.10	0	1.86	1.86	0	0	0	0	1.86	1.86
5 – 9	79.60	0	3.09	3.09	0	0	0	0	3.09	3.09
10 - 14	74.90	0	3.40	3.40	0	6.41	6.41	0	9.82	9.82
15 - 19	69.60	0	2.33	2.33	0	11.70	11.70	0	14.03	14.03
20 - 24	64.60	0	10.32	10.32	0	5.52	5.52	0	15.84	15.84
25 - 29	59.60	54.67	8.28	62.95	0	11.30	11.30	0	19.58	19.58
30 - 34	54.60	0	16.07	16.07	48.71	18.43	67.15	56.67	34.51	89.18
35 - 39	49.60	45.55	25.70	71.22	141.70	31.31	172.99	145.52	56.98	202.50
40 - 44	44.60	116.92	91.51	208.43	121.56	63.15	184.71	175.78	154.66	330.44
45 - 49	39.60	390.03	162.46	552.50	390.11	140.61	530.73	415.46	303.10	718.56
50 - 54	34.60	641.38	344.27	985.65	651.14	299.87	951.01	1075.15	644.15	1719.30
55 – 59	29.60	1,193.0	523.05	1,716.05	1703.93	460.32	2164.25	1936.98	983.37	2920.35
60 - 64	24.60	1,637.89	788.24	2,426.14	2264.83	545.56	2810.40	3317.62	1,333.80	4651.42

65 - 69	19.60	2,214.79	976.50	3,191.29	2479.26	586.72	3065.98	4459.86	1,563.22	6023.08
70 - 74	14.60	1,868.90	787.97	2,656.86	2005.65	433.10	2438.71	4644.39	1,221.04	5865.43
75 - 79	9.60	1,530.41	822.0	2,352.36	1251.38	387.53	1638.92	3372.40	1,209.48	4581.88
80 - 85	4.60	299.60	316.96	616.56	233.57	151.10	384.65	1644.35	468.04	2112.39
≥85	1.60	0.77	104.51	105.29	1.29	46.09	47.38	44.89	150.61	195.5
Total		9,993.91	4,988.52	14,982.38	11,293.13	3,198.68	14,491.81	21,287.04	8,187.20	29,474.24

Figure S4. Sensitivity analysis: Exclusion of age-adjustment in CCI, outliers (A) and mortality rate across the study period (B).

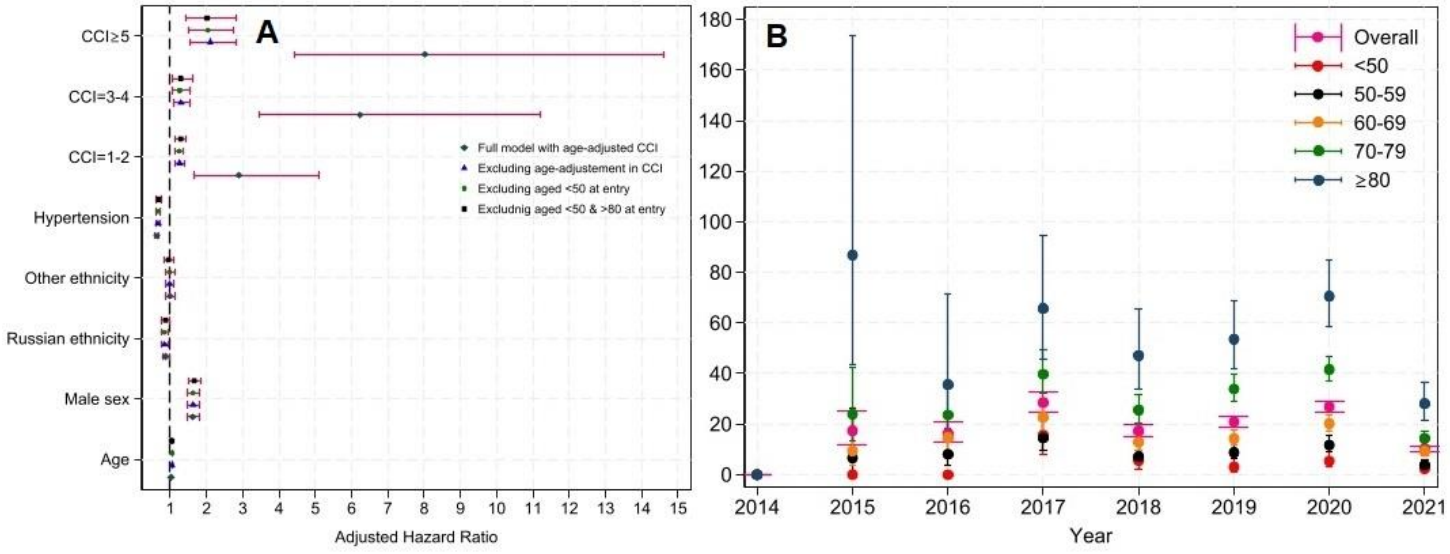


Figure S5. Survival probability by sex, ethnicity, CCI and hypertension (following propensity score matching (3,690 hypertensive vs 3,690 non-hypertensive)).

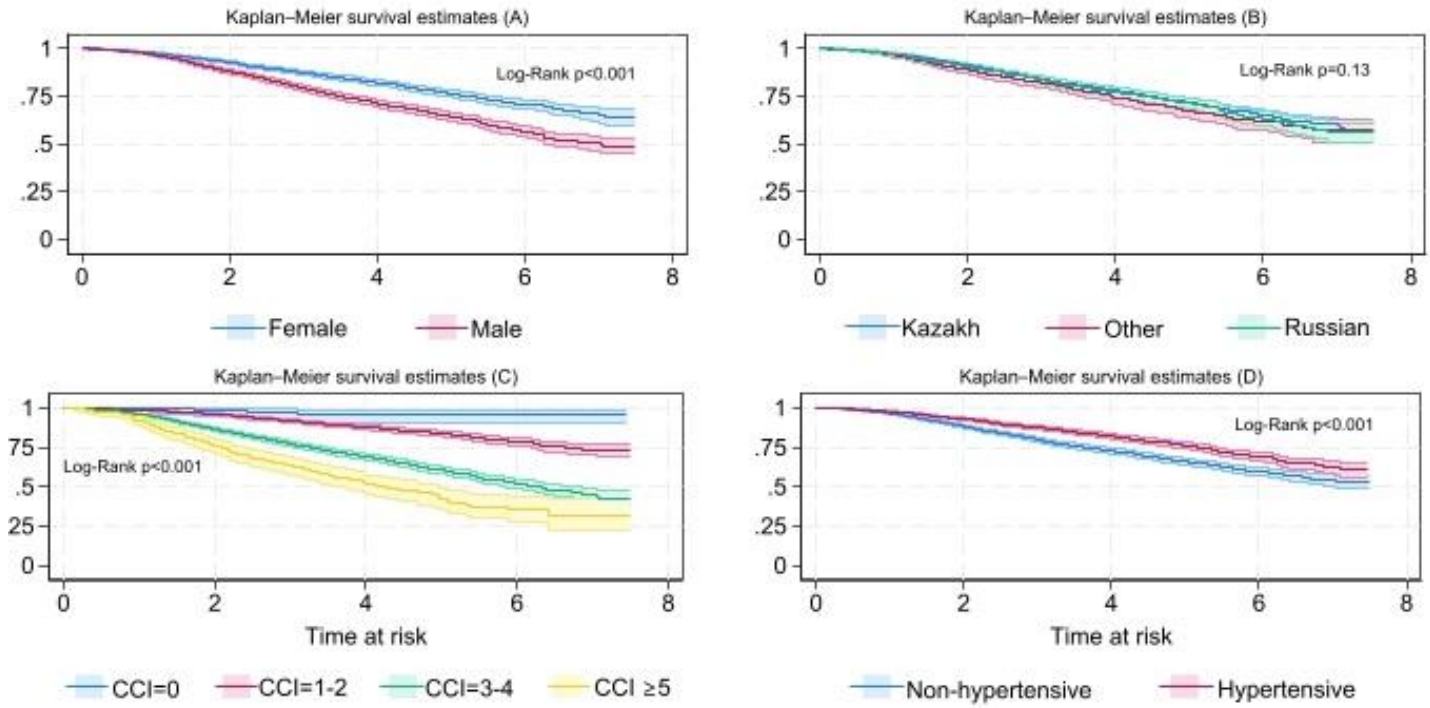
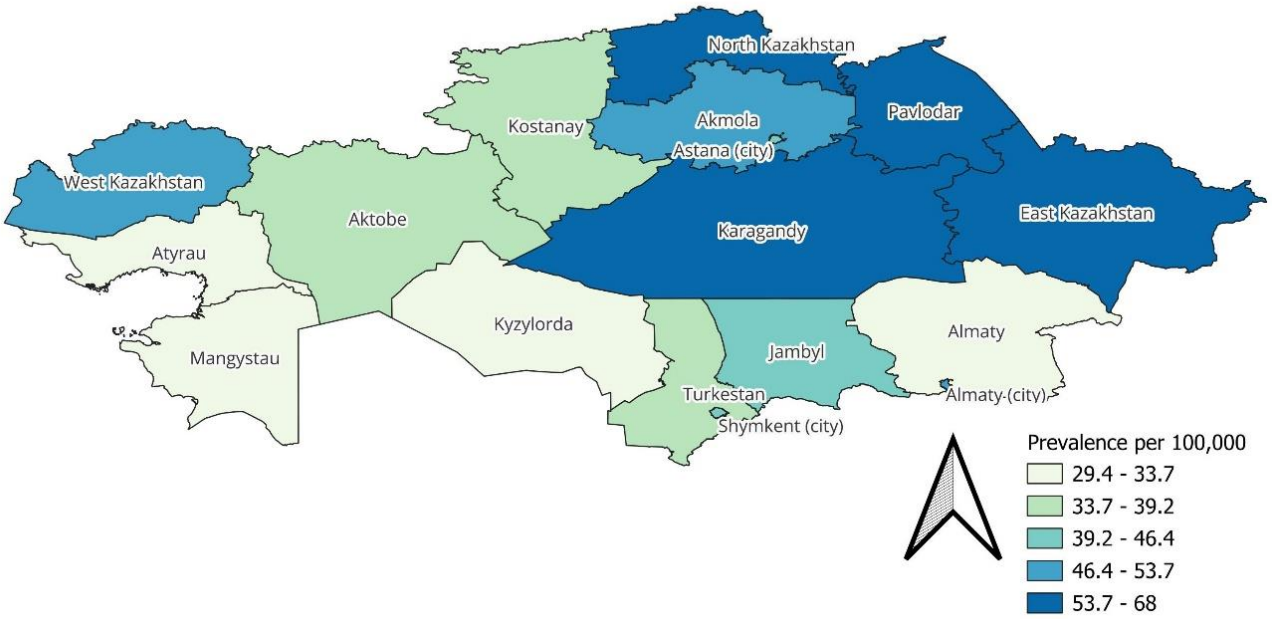


Figure S6. Region-adjusted prevalence of PD in 2021.



Ethics approval and consent to participate

The Nazarbayev University Institutional Review Ethics Committee accepted this study (NU-IREC 490/18112021) and waived the requirement for informed consent.