scientific reports

Check for updates

OPEN

Association of waist circumference with all cause mortality in Parkinson's disease

Jee Hyun Suh[1], Seok-Jae Heo[2], Yong Wook Kim[3], Sang Chul Lee[3] & Seo Yeon Yoon[3,4]✉

Despite many previous studies on the association between metabolic syndrome and Parkinson disease (PD), only few studies have investigated the association between waist circumference (WC) and PD. The aim of this study is to investigate the association between WC and all-cause mortality in patients with PD. Among the whole nationwide population data from Korea National Health Insurance Service, newly diagnosed PD (ICD-10 code G20 and rare intractable disease registration code V124), between 2008 and 2017, were selected. All-cause mortality was the primary outcome. Anthropometric data, including WC and body mass index (BMI) were obtained from health screening data. The Cox proportional hazards model was used to assess mortality risk according to WC. Among the 22,118 patients with PD, 9,179 (41.50%) died during the 10-year follow-up period. WCs < 70 cm among males and < 65 cm among females were significantly associated with increased mortality in patients with PD (HR = 1.19, 95% CI, 1.05–1.34). After adjusting for BMI, WC of ≥ 90 cm in males or ≥ 85 cm in females, which are the criteria for central obesity, increased mortality risk significantly (M 90–100, F 85–95: HR = 1.13, 95% CI, 1.05–1.22; M ≥ 100, F ≥ 95: HR = 1.50, 95% CI, 1.33–1.68). The association between WC and PD mortality revealed a J-shaped pattern among males and a U-shaped pattern among females. Central obesity is a significant risk factor for mortality in patients with PD after adjusting for BMI. Our results suggest that management of WC is crucial for PD patients and that BMI should be considered in the WC management plan for mortality in PD.

Keywords Waist circumference, Body mass index, Parkinson disease, Mortality

Abbreviations

PD	Parkinson disease
BMI	Body mass index
WC	Waist circumference
MetS	Metabolic syndrome
NHIS	National Health Insurance Service
NHSP	Health screening program
SD	Standard deviation
HR	Hazard ratio

Idiopathic Parkinson disease (PD) is the second most common neurodegenerative disease after Alzheimer disease, with an incidence of 80.4–678 per 100,000 person-years[1–4]. PD may be caused by genetic factors or may be idiopathic, with idiopathic PD accounting for 85–90% of PD cases[5]. The incidence rate of PD is highest in the 7th decade of life, with age being the greatest risk factor for PD[6]. As the population ages, the number of patients with PD rapidly increases, along with an increased socioeconomic burden. The etiopathology of idiopathic PD is multifactorial[7]. In recent decades, studies have reported that components of metabolic syndrome (MetS), including abdominal obesity, impaired fasting glucose, high blood pressure, dyslipidemia, low cholesterol level, and stain use are associated with PD[8–14]. PD and MetS are suggested to have overlapping pathophysiological mechanisms, encompassing insulin resistance, persistent inflammation, and oxidative stress[8].

Several studies have investigated the risk of developing PD in association with MetS. Diabetes mellitus (DM), glycemic status, dyslipidemia, and hypertension are associated with increased PD risk. Given the characteristic

[1]Department of Rehabilitation Medicine, Seoul National University Bundang Hospital, Seongnam-si, Gyeonggi-do, Korea. [2]Department of Biostatistics and Computing, Yonsei University Graduate School, Seoul, Republic of Korea. [3]Department and Research Institute of Rehabilitation Medicine, Yonsei University College of Medicine, 50-1 Yonsei-ro Seodaemun-gu, Seoul 03722, Republic of Korea. [4]Institute for Innovation in Digital Healthcare, Yonsei University, Seoul, Republic of Korea. ✉email: syyoon23@yuhs.ac

nature of PD, factors influencing its onset may also have an impact on the progression of PD[15]. However, the number of studies on how the components of MetS may influence the progression of PD is relatively small. The presence of DM has been suggested to be associated with faster motor progression and cognitive decline in patients with PD[16]. Dyslipidemia was negatively correlated with PD mortality in a previous nationwide cohort study[17].

Abdominal obesity is a component of the MetS cluster and is typically assessed by measuring waist circumference (WC). Irrespective of other fat deposits, abdominal (visceral) obesity is a major risk factor for systemic inflammation, hyperlipidemia, insulin resistance, and cardiovascular disease[18]. The association between WC and PD has rarely been investigated. To our knowledge, only one study has investigated the association between WC and PD development, suggesting that a high WC increases the risk of PD[11]. However, the association between WC and mortality in PD has not yet been elucidated. Therefore, this study aimed to investigate the association between baseline WC at diagnosis and all-cause mortality rate in patients with idiopathic PD using large nationwide population-based data. We also investigated the association between WC and mortality in patients with PD differentiated by sex and body mass index (BMI).

Results

Participant characteristics

The baseline characteristics of the patients with PD are presented in Table 1. Males and females in the highest category of WC were more likely to be older; have higher Charlson comorbidity index (CCI), BMI, blood pressure, serum total cholesterol, triglyceride, low-density lipoprotein, and fasting glucose levels; and have lower serum high-density lipoprotein levels than those with smaller WCs (Table 1).

The baseline characteristics of the age- and sex- matched cohort are presented in Supplementary Table 1.

Association between WC and All-Cause mortality

Among 22,118 patients with PD, 9,179 (41.50%) died during the 10-year follow-up period. The HRs for all-cause mortality associated with the WC categories are shown in Table 2. WCs < 70 cm in males and < 65 cm in females were significantly associated with increased mortality in all models. HRs for mortality in PD patients with WC of ≥ 90 cm among males or ≥ 85 cm among females revealed different results after adjustment for confounding

Variables	Waist circumference					
	M < 70 F < 65	M 70-80 F 65–75	M 80-90 F 75–85	M90-100 F 85–95	M > 100 F > 95	*p*-value
N (%)	590 (2.7)	4,569 (20.7)	9,819 (44.4)	5,834 (26.4)	1,306 (5.9)	
Age (years)	68.70 ± 11.42	68.17 ± 10.37	68.84 ± 9.00	69.66 ± 8.21	69.98 ± 8.20	< 0.001
Sex						< 0.001
Male	261 (44.2)	2,013 (44.1)	4,447 (45.3)	2,353 (40.3)	377 (28.9)	
Female	329 (55.8)	2,556 (55.9)	5,372 (54.7)	3,481 (59.7)	929 (71.1)	
Low income level (lower 25%)	110 (18.6)	844 (18.5)	1,650 (16.8)	957 (16.4)	214 (16.4)	0.038
Residential area (urban)	230 (39.0)	1,811 (39.6)	3,878 (39.5)	2,231 (38.2)	484 (37.1)	0.262
Insurance type						< 0.001
National health insurance	568 (96.3)	4,456 (97.5)	9,661 (98.4)	5,729 (98.2)	1,274 (97.5)	
Medical aid	22 (3.7)	113 (2.5)	158 (1.6)	105 (1.8)	32 (2.5)	
Charlson comorbidity index	2.73 ± 2.21	2.67 ± 2.20	2.99 ± 2.34	3.28 ± 2.38	3.69 ± 2.44	< 0.001
†Hypertension	279 (47.3)	2,299 (50.3)	5,953 (60.6)	4,152 (71.2)	1,025 (78.5)	< 0.001
†Dyslipidemia	202 (34.2)	1,774 (38.8)	4,559 (46.4)	3,105 (53.2)	755 (57.8)	< 0.001
†Pneumonia	62 (10.5)	365 (8.0)	734 (7.5)	472 (8.1)	102 (7.8)	0.082
†Depression	174 (29.5)	1,173 (25.7)	2,617 (26.7)	1,627 (27.9)	398 (30.5)	0.002
Current smoker	46 (7.8)	345 (7.6)	697 (7.1)	333 (5.7)	67 (5.1)	< 0.001
Heavy alcohol drinker	8 (1.4)	108 (2.4)	237 (2.4)	165 (2.8)	23 (1.8)	0.055
Regular exercise	125 (21.2)	1,324 (29.0)	2,902 (29.6)	1,657 (28.4)	282 (21.6)	< 0.001
Body mass index (kg/m^2)	18.59 ± 2.40	20.92 ± 2.09	23.46 ± 2.19	25.97 ± 2.39	28.90 ± 3.01	< 0.001
Systolic blood pressure (mmHg)	120.09 ± 16.36	123.61 ± 16.24	126.86 ± 15.92	129.25 ± 15.81	131.18 ± 16.16	< 0.001
Diastolic blood pressure (mmHg)	74.45 ± 10.26	75.32 ± 10.14	76.93 ± 10.00	77.90 ± 10.10	78.75 ± 10.37	< 0.001
Laboratory findings						
Total cholesterol (mg/dL)	176.69 ± 36.16	187.03 ± 38.75	190.55 ± 43.29	192.66 ± 50.29	197.47 ± 83.02	< 0.001
Triglyceride (mg/dL)	94.15 ± 44.21	111.67 ± 63.51	131.99 ± 79.02	147.89 ± 82.26	160.57 ± 96.45	< 0.001
LDL (mg/dL)	101.18 ± 31.30	111.47 ± 50.75	113.45 ± 49.09	114.78 ± 64.44	116.77 ± 86.03	< 0.001
HDL (mg/dL)	56.50 ± 15.62	55.23 ± 25.02	52.11 ± 24.02	50.68 ± 23.23	50.89 ± 27.39	< 0.001
Fasting glucose	97.49 ± 24.15	101.60 ± 26.44	104.64 ± 29.53	109.18 ± 33.02	113.80 ± 37.46	< 0.001

Table 1. Characteristics of participants. Values are presented as mean ± SD or number (%). HDL, high-density lipoprotein; LDL, low-density lipoprotein. †Other co-morbidities not included in Charlson comorbidity index.

	PD	Mortality	Person-years	Incidence rate	Model 1	*p*-value	Model 2	*p*-value	Model 3	*p*-value
Total										
M < 70, F < 65	590	322	4254.3	75.7	1.44 (1.28–1.62)	< 0.001	1.45 (1.29–1.63)	< 0.001	1.19 (1.05–1.34)	0.005
M 70–80, F 65–75	4569	2031	37653.0	53.9	reference		reference		reference	
M 80–90, F 75–85	9819	3953	84448.4	46.8	0.86 (0.82–0.91)	< 0.001	0.83 (0.79–0.88)	< 0.001	0.99 (0.94–1.05)	0.808
M 90–100, F 85–95	5834	2316	50716.7	45.7	0.84 (0.79–0.89)	< 0.001	0.79 (0.75–0.84)	< 0.001	1.13 (1.05–1.22)	0.002
M ≥ 100, F ≥ 95	1306	557	11231.2	49.6	0.91 (0.83-1.00)	0.061	0.89 (0.81–0.98)	0.020	1.50 (1.33–1.68)	< 0.001
Male										
< 70	261	161	1754.4	91.8	1.32 (1.12–1.56)	< 0.001	1.36 (1.15–1.6)	< 0.001	1.07 (0.91–1.27)	0.424
70–80	2013	1090	15282.0	71.3	reference		reference		reference	
80–90	4447	2157	35603.1	60.6	0.84 (0.78–0.91)	< 0.001	0.85 (0.79–0.91)	< 0.001	1.05 (0.97–1.13)	0.268
90–100	2353	1135	18873.0	60.1	0.84 (0.77–0.91)	< 0.001	0.81 (0.74–0.88)	< 0.001	1.22 (1.1–1.36)	< 0.001
≥ 100	377	202	2873.3	70.3	0.99 (0.85–1.15)	0.873	0.94 (0.81–1.09)	0.383	1.75 (1.46–2.1)	< 0.001
Female										
< 65	329	161	2499.9	64.4	1.58 (1.33–1.86)	< 0.001	1.54 (1.3–1.82)	< 0.001	1.29 (1.09–1.53)	0.003
65–75	2556	941	22371.0	42.1	reference		reference		reference	
75–85	5372	1796	48845.4	36.8	0.87 (0.8–0.94)	< 0.001	0.81 (0.75–0.88)	< 0.001	0.94 (0.87–1.03)	0.189
85–95	3481	1181	31843.7	37.1	0.87 (0.8–0.95)	0.002	0.78 (0.71–0.85)	< 0.001	1.05 (0.94–1.17)	0.373
≥ 95	929	355	8357.9	42.5	1.01 (0.89–1.14)	0.928	0.86 (0.76–0.97)	0.860	1.32 (1.13–1.53)	< 0.001

Table 2. Risk of All-Cause mortality among individuals with Parkinson's disease by waist circumference. Mortality rate is the incidence of mortality per 1000 person-years. Model 1: unadjusted. Model 2: adjusted for age, sex, Income level, and residential area. Model 3: adjusted for age, sex, Income level, residential area, comorbidities, lifestyle factors, body mass index, and disability grade.

variables. In models 1 and 2, mortality risk was significantly decreased at WCs of ≥ 80 cm among males and ≥ 75 cm among females. However, after adjusting for BMI and disability grades in model 3, WCs of ≥ 90 cm among males and ≥ 85 cm among females showed significant association with increased mortality in patients with PD (M 90–100, F 85–95: HR = 1.13, 95% CI, 1.05–1.22; M ≥ 100, F ≥ 95: HR = 1.50, 95% CI, 1.33–1.68).

In the age- and sex- matched cohort, there was a significant association between WC and mortality only in centrally obese individuals, with an increased trend of mortality in this population (M 90–100, F 85–95: HR = 1.12, 95% CI, 1.00–1.22; M ≥ 100, F ≥ 95: HR = 1.78, 95% CI, 1.48–2.14, Supplementary Table 2).

Association between WC and All-Cause mortality by sex

In the subgroup analyses by sex, the HRs for all-cause mortality according to WC categories showed similar patterns to those of all patients with PD after adjusting for variables. However, in Model 3, there were some differences in the association between mortality and WC < 70 cm among males and 85–95 cm among females in Model 3. There were no significant associations between mortality and WC in males with < 70 cm (HR = 1.07, 95% CI, 0.91–1.27) and females with WC 85–95 cm (HR = 1.05, 95% CI, 0.94–1.17). In restricted cubic spline plots of the association between WC and all-cause mortality, data from males showed a J-shaped pattern, whereas those from females showed a U-shaped pattern (Fig. 1).

In the age- and sex- matched cohort, the mortality risk was increased only in males with WC ≥ 90 cm (90–100: HR = 1.24, 95% CI, 1.06–1.462; ≥100: HR = 1.96, 95% CI, 1.47–2.61) and females with WC ≥ 95 cm (HR = 1.57, 95% CI, 1.22–2.01). The association between WC and mortality showed an overall J-shaped pattern in both males and females in the matched cohort (Supplementary Fig. 1).

Subgroup analyses

After stratifying BMI to three categories (< 18.5, 18.5 ≤ BMI < 25, ≥25 kg/m^2), analyses were conducted on the risk of all-cause mortality among individuals with PD based on WC (Table 3). There were no statistically significant differences in mortality based on WC in the groups with either low or high BMI (BMI < 18.5 kg/m^2 or BMI ≥ 25 kg/m^2). However, in the group of 18.5 ≤ BMI < 25 kg/m^2, increases in WC of ≥ 90 cm in males or ≥ 85 cm in females were observed to be statistically significantly associated with an increase in mortality risk. The results of the subgroup analyses by lifestyle factors and comorbidities for the association between WC and mortality in patients with PD are presented in Supplementary Table 3. The interaction terms for all the variables were not significant.

Additionally, we evaluated the all-cause mortality based on the presence of obesity and central obesity. When individuals without both obesity and central obesity were used as a reference group, presence of central obesity revealed a significant association with increased mortality in patients with PD (HR = 1.16, 95% CI, 1.09–1.23). Overall, the presence of obesity significantly reduced mortality risk, with a slight increase of mortality risk when central obesity was combined (with central obesity: HR = 0.83, 95% CI, 0.73–0.93; without central obesity: HR = 0.80, 95% CI, 0.73–0.88) (Fig. 2).

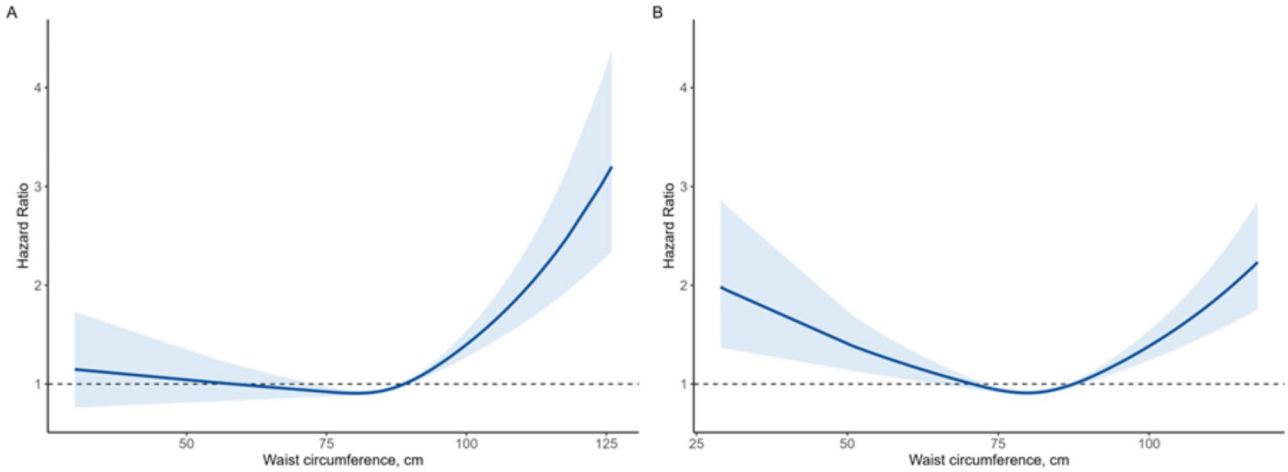

Fig. 1. Restricted cubic spline plots of the association between waist circumference (WC) and all-cause mortality in individuals with Parkinson disease (PD). (**A**) Male and (**B**) Female.

	PD	Mortality	Person-years	Incidence rate	Model 1	*p*-value	Model 2	*p*-value	Model 3	*p*-value
BMI < 18.5										
M < 70, F < 65	306	186	2,108.7	88.2	0.86 (0.72–1.03)	0.102	0.97 (0.81–1.17)	0.780	0.87 (0.72–1.06)	0.166
M 70–80, F 65–75	490	333	3,269.2	101.9	reference		reference		reference	
M 80–90, F 75–85	154	115	926.0	124.2	1.25 (1.01–1.54)	0.043	1.06 (0.85–1.32)	0.596	1.11 (0.89–1.39)	0.366
M 90–100, F 85–95	14	11	89.0	123.6	1.22 (0.67–2.22)	0.521	0.96 (0.52–1.75)	0.891	1.08 (0.59–1.99)	0.803
M ≥ 100, F ≥ 95	1	0	9.6	0.0						
18.5 ≤ BMI < 25										
M < 70, F < 65	276	130	2,075.8	62.6	1.28 (1.07–1.53)	0.008	1.36 (1.14–1.63)	< 0.001	1.17 (0.98–1.4)	0.088
M 70–80, F 65–75	3,961	1,663	33,258.7	50.0	reference		reference		reference	
M 80–90, F 75–85	7,339	3,139	62,131.4	50.5	1.01 (0.95–1.07)	0.722	0.92 (0.87–0.98)	0.006	1.04 (0.98–1.11)	0.228
M 90–100, F 85–95	1,862	930	15,143.9	61.4	1.24 (1.15–1.34)	< 0.001	1.01 (0.94–1.10)	0.733	1.21 (1.10–1.32)	< 0.001
M ≥ 100, F ≥ 95	95	57	707.9	80.5	1.65 (1.27–2.15)	< 0.001	1.24 (0.95–1.62)	0.109	1.38 (1.06–1.81)	0.019
BMI ≥ 25										
M < 70, F < 65	8	6	69.8	85.7	2.77 (1.17–6.59)	0.021	1.36 (0.57–3.23)	0.487	1.31 (0.55–3.12)	0.547
M 70–80, F 65–75	118	35	1,125.1	31.1	reference		reference		reference	
M 80–90, F 75–85	2,326	699	21,391.0	32.7	1.05 (0.74–1.47)	0.800	1.03 (0.73–1.44)	0.876	1.01 (0.72–1.42)	0.942
M 90–100, F 85–95	3,958	1,375	35,483.8	38.7	1.25 (0.89–1.74)	0.198	1.11 (0.80–1.56)	0.534	1.07 (0.76–1.50)	0.696
M ≥ 100, F ≥ 95	1,210	500	10,513.7	47.6	1.54 (1.10–2.17)	0.013	1.38 (0.98–1.95)	0.064	1.29 (0.91–1.83)	0.159

Table 3. Risk of All-Cause mortality among individuals with Parkinson's disease by waist circumference stratified by body mass index. Mortality rate is the incidence of mortality per 1000 person-years. Model 1: unadjusted. Model 2: adjusted for age, sex, Income level, and residential area. Model 3: adjusted for age, sex, Income level, residential area, comorbidities, lifestyle factors, and disability grade.

Discussion

In this nationwide cohort study using Korean National Health Insurance Service (NHIS) data, we analyzed 22,118 patients with idiopathic PD, diagnosed based on International Classification of Diseases, 10th Revision (ICD-10) codes and rare intractable disease registration codes, to investigate the association between WC and all-cause mortality. WCs < 70 cm in males and < 65 cm in females were significantly associated with increased mortality in patients with PD. WC of ≥ 80 cm in males or ≥ 75 cm in females was significantly associated with decreased mortality in model 1 and model 2. However, after adjusting for BMI and disability grades in model 3, WC of ≥ 90 cm in males or ≥ 85 cm in females, which are the criteria for central obesity, increased all-cause mortality significantly. In the analysis considering both obesity and central obesity, central obesity was associated with an increased mortality risk, whereas obesity decreased the mortality risk. In the sex-stratified analysis, the association between WC and mortality revealed a J- and U-shaped pattern in males and females, respectively.

MetS is a prevalent and increasing public health issue linked to various chronic diseases on a global scale. The constituents of MetS encompass central/abdominal obesity, systemic hypertension, DM, and atherogenic dyslipidemia, forming what is commonly referred to as the "fatal quartet." Recently, numerous studies have

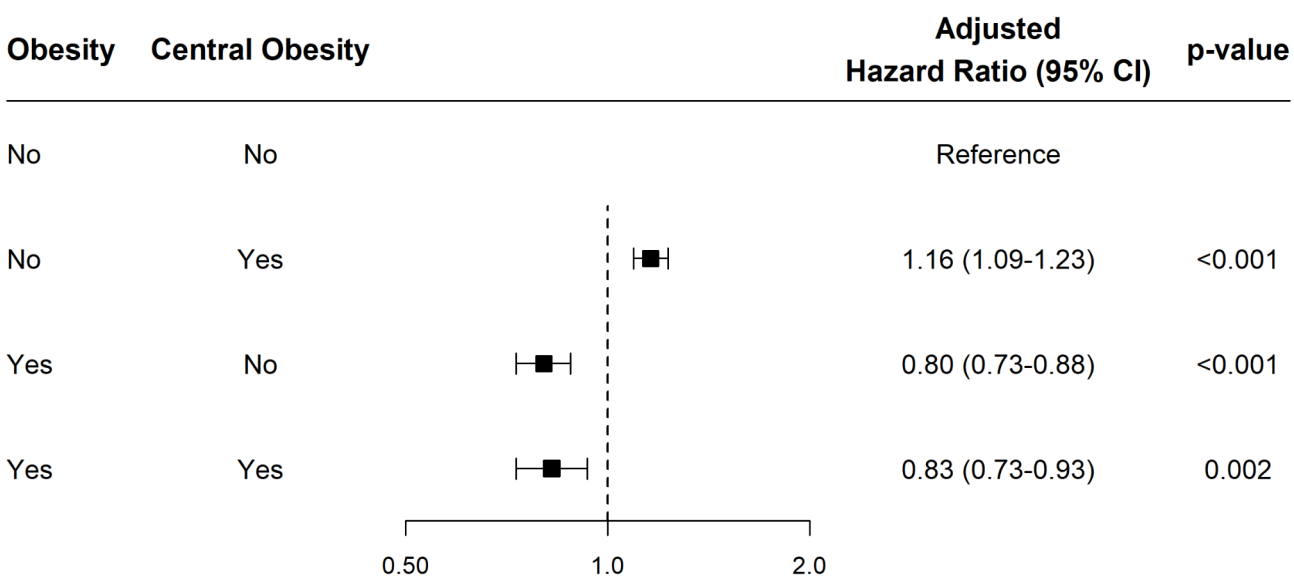

Fig. 2. Adjusted hazard ratios with 95% confidence intervals for all-cause mortality in individuals with Parkinson disease (PD) according to obesity and central obesity.

explored the association between MetS and PD. Hypotheses of possible links between MetS and PD have been proposed, such as oxidative stress, altered lipid pathways, increased inflammation, and the induction of abnormal protein deposition,[19 20] which enhance the understanding of the multifactorial etiologies of PD. The risk of PD significantly increases with the degree of hyperglycemia and the duration of diabetes[21]. Hypertension also has been suggested to increase the risk of PD[22,23]. Although the results are controversial, dyslipidemia has been suggested to be associated with the risk of PD[24,25]. Despite numerous previous studies on the association between MetS and PD risk, the number of studies on the association between MetS and PD progression is relatively small[16,17]. Our previous study showed that dyslipidemia was negatively correlated with mortality in PD[17]. DM has been identified as a negative prognostic factor linked to accelerated motor progression and cognitive decline in PD[16]. In our previous research, we observed an inverse dose-response association between BMI and mortality in patients with PD[15].

Although central obesity is an essential component of MetS, the association between WC and PD has rarely been investigated. A previous study suggested that higher WC and abdominal obesity were associated with an increased risk of PD[11]. In the study, insulin resistance was suggested as a possible link between the two conditions. Central obesity causes insulin resistance, which leads to neurodegeneration due to an increase in intracellular protein aggregates in the substantia nigra[26]. Recently, Lixisenatide, a glucagon-like peptide-1 receptor agonist used in diabetes treatment, has been suggested to help slow the progression of motor disability in patients with PD[27]. There has been no research on the association between WC and disease progression in patients with PD. Therefore, we investigated the association between WC and disease progression in PD patients using large-scale data. In models 1 and 2, WC of ≥ 80 cm in males or ≥ 75 cm in females was associated with decreased mortality; however, in model 3, which further adjusted for BMI and disability grades, central obesity showed significant association with increased mortality. WC is significantly correlated with BMI and body weight[28,29]; therefore, it is essential to consider influence of BMI when examining the association between WC and mortality in patients with PD. In our study, the confounding factor that affected the results between models 2 and 3 was BMI (data not shown).

We performed several additional analyses to determine the association between WC and mortality stratified by BMI or central obesity status. In the BMI analysis, there was no significant association between WC and mortality in the high and low BMI groups. However, in the normal-weight and overweight groups, central obesity significantly increased the mortality risk in PD. In the stratified analysis by obesity and central obesity, central obesity increased mortality risk. Obesity reduces PD mortality, with a slight increase in mortality when combined with central obesity. A high BMI can influence insulin levels, and this may have an inverse response on the mortality of PD by playing a beneficial role in dopaminergic neurodegeneration[30]. On the other hand, high WC leads to the accumulation of visceral adipose tissue. This affects the endocrine organs that secrete adipokines such as leptin and adiponectin. These adipokines, in turn, affect neurodegeneration[31,32]. Based on our results, a high BMI has a protective effect on PD mortality, whereas a high WC has a detrimental effect.

WC has been presented as an important risk factor for mortality in older adults in the United States, and a positive association was observed, regardless of BMI[33]. In a preceding study with a population aged 51 to 72 years, high WC was associated with an increased risk of mortality both in males and females[34]. In the study, the relationship between WC and mortality exhibited a J-shaped pattern only in males, while in females, there was an increasing trend in mortality with an increase in WC[34]. In a previous study conducted in the Chinese general population, the association between WC and mortality revealed a J-shaped pattern[35]. In this study we included an age- and sex- matched comparison cohort to examine the association between WC and mortality in general

population, and the results were similar to those in the Chinese population, showing an overall J-shaped pattern in both males and females. For patients with PD, there was a J-shaped relationship between WC and mortality in males, consistent with previous research in the general population. However, in females, the relationship was not linear or J-shaped but U-shaped in this study, which is somewhat different from that in the general population. According to previous studies, PD progression varies by sex[36,37]. Female patients experience a higher risk of dyskinesia, which, in turn, increases the risk of undernutrition[36,38]. Another previous study showed that predictors of weight loss early in the course of PD include female sex[39]. In our previous cohort study in Korean populations, an inverse dose-response association between BMI and mortality was only observed in female patients with PD[15]. Extremely low WC group might have include individuals who have poor nutritional status and advanced disease progression[40,41], which could be a possible reason for a U-shaped relationship between WC and mortality even after adjusting for BMI.

Limitations

Our study had several limitations. First, PD was defined by ICD-codes and rare intractable disease registration codes without clinical or imaging data; hence, we cannot exclude misclassification. Although the use of PD diagnosis codes in electronic health record has been suggested to be insufficiently accurate, it can be most improved by removing other parkinsonism codes[42]. Therefore, in this study, we excluded patients with other types of parkinsonism, such as atypical or secondary parkinsonism, to ensure the homogeneity of participants. Second, information related to WC, such as body composition and nutritional status, could not be obtained from the claims-based database. Third, although we tried to adjust for many variables that could be related to mortality in patients with PD, symptoms such as dysphagia and gait disturbances could not be included in the analysis. Fourth, we only examined the association between WC and all-cause mortality risk and not cause-specific mortality. Finally, this study included only a Korean population, making it difficult to generalize our results to other ethnicities.

Conclusion

In conclusion, in this large nationwide cohort study comprising South Koreans, we found that central obesity was a significant risk factor for increased mortality in patients with PD after adjusting for BMI. Although obesity was associated with reduced PD mortality, combined central obesity slightly increased the risk of mortality in obese patients with PD. There was a J-shaped pattern among males and a U-shaped pattern among females regarding the association between WC and PD mortality. Our results underscore the importance of WC management for reducing mortality in patients with PD, and an individualized approach to WC management that considers BMI is needed.

Methods

Data source

We used data from the Korean NHIS, a single, mandatory universal health insurance system launched in 2000. All individuals born in Korea are assigned a unique resident registration number and included in the NHIS system. The database contains the medical records of the entire Korean population covered by the obligatory NHIS and Medical Aid programs. The NHIS database contains an extensive medical dataset, including diagnostic codes according to ICD-10 codes, procedures, prescription drugs, demographics, and the use of medical clinics. The NHIS provides claims and health screening examination data. The NHIS provides a free biannual national health screening program (NHSP) for all beneficiaries aged ≥ 40 years and for workplace subscribers of all ages. In addition to self-report questionnaires and laboratory tests, anthropometric measurements are obtained.

Study population

In 2006, the Korean government implemented a registration program for rare intractable diseases to reduce co-payments by providing financial support for patients' medical expenses. The rare intractable disease code for PD is V124. To be registered in the program with PD, the physician must confirm the patient meets strict criteria, which are almost the same as the those of the UK Parkinson's Disease Society Brain Bank. In addition, the NHIS program conducts regular cross-checking by reviewing medical records to prevent miscoding or inaccurate medical claims; therefore, the rare intractable diseases registry data are considered valid and reliable. In this study, we selected individuals newly diagnosed with PD (ICD-10 code G20 and rare intractable disease code V124) between January 2008 and December 2017. We then excluded individuals (1) with a combined diagnosis of secondary parkinsonism or atypical parkinsonism (ICD-10 codes G21-G23) and (2) diagnosed with PD before 2009, to include only new-onset PD. Among them, those who had participated in the NHSP at least once within two years after the initial diagnosis of PD were selected. Individuals with missing data were excluded. Finally, we longitudinally followed 22,118 individuals with PD to investigate the association between WC and mortality in patients with PD. In addition, we included an age- and sex- matched comparison cohort to compare the results with PD participants. This study was approved by the Institutional Review Board of the tertiary hospital (IRB No: 4-2023-1428), which waived the requirement for obtaining informed consent from patients. All research was conducted in accordance with the relevant guidelines and regulations of the IRB.

Assessment of waist circumference

Anthropometric data, including WC, were obtained from the health screening data. WC was measured using a soft, non-stretchable tape at the narrowest point between the inferior border of the rib cage and the iliac crest by trained health technicians. We classified WC into following five categories: <70, 70–80, 80–90, 90–100, and

≥ 100 cm in males and the following: <65, 65–75, 75–85, 85–95, ≥ 95 cm in females. Central obesity was defined as WC ≥ 90 cm in males or WC ≥ 85 cm in females as per the Korean obesity guidelines[43].

Other variables

The primary outcome variable was all-cause mortality, evaluated using nationwide death certificate data from the Korea National Statistical Office. Individuals who paid the bottom 25% of the NHI premiums were classified as belonging to the low-income group. Residential areas were categorized into urban and rural. Lifestyle factors were assessed using a self-report questionnaire from the NHSP. Current smoking was defined as having smoked ≥ 100 cigarettes in their lifetime or currently. Alcohol consumption was categorized based on the weekly frequency of drinking as none, mild drinking (≤ 4 times/week), or heavy drinking (≥ 5 times/week). Regular exercise was defined as vigorous-intensity physical activity ≥ 3 days/week or moderate-intensity physical activity ≥ 5 days/week. BMI was calculated as weight (kg) divided by height in meters squared (m^2), and obesity was defined as a BMI ≥ 25. Blood samples were collected after overnight fasting for at least 8 h. CCI and other comorbidities were identified based on the corresponding disease diagnostic codes. The CCI is the most widely studied morbidity index covering 19 diseases, including congestive heart failure, myocardial infarction, cerebrovascular disease, peripheral vascular disease, connective tissue disease, chronic lung disease, ulcer, chronic liver disease, severe liver disease, dementia, diabetes, hemiplegia, moderate or severe kidney disease, tumor, leukemia, lymphoma, moderate or metastatic solid tumor, and acquired immunodeficiency syndrome. Disability registration from brain impairment was used as a proxy for PD severity.

Statistical analyses

Analysis of variance (ANOVA) was performed for continuous variables, and the chi-square test was performed for categorical variables to examine the characteristics of patients with PD according to WC groups. Demographic and medical data were presented as mean ± standard deviation (SD) for continuous variables and as frequency (percentage) for categorical variables. The mortality rate was calculated as the number of deaths divided by person-years of follow-up and reported per 1000 person-years. Cox proportional hazards models were employed to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) according to the WC groups using the three models. Model 1 was unadjusted. Model 2 was adjusted for age, sex, income level, and residential location. Model 3 was additionally adjusted for comorbidities, lifestyle factors, BMI, and disability grade. Restricted cubic spline analysis in the Cox proportional hazards model was used to determine the nonlinear relationship between WC and all-cause mortality. Subgroup analyses were performed according to lifestyle factors and comorbidities. All statistical analyses were performed using SAS for Windows (version 9.4; SAS Institute Inc., Cary, NC, USA), and statistical significance was defined as a two-tailed p-value of < 0.05.

Data availability

The data that support the findings of this study are available from Korea NHIS Big Data Operations Department but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the corresponding authors upon reasonable request and with permission of the Institutional Review Board and the Korea NHIS Big Data Operations Department (https://nhiss.nhis.or.kr/bd/ay/bdaya 001 iv.do).

Received: 23 August 2024; Accepted: 3 March 2025
Published online: 18 March 2025

References

1. Van Den Eeden, S. K. et al. Incidence of Parkinson's disease: Variation by age, gender, and race/ethnicity. *Am. J. Epidemiol.* **157**, 1015–1022. https://doi.org/10.1093/aje/kwg068 (2003).
2. von Campenhausen, S. et al. Prevalence and incidence of Parkinson's disease in Europe. *Eur. Neuropsychopharmacol.* **15**, 473–490. https://doi.org/10.1016/j.euroneuro.2005.04.007 (2005).
3. Kang, S. H. et al. Incidence of Parkinson's disease and modifiable risk factors in Korean population: A longitudinal follow-up study of a nationwide cohort. *Front. Aging Neurosci.* **15**, 1094778. https://doi.org/10.3389/fnagi.2023.1094778 (2023).
4. Baldereschi, M. et al. Parkinson's disease and parkinsonism in a longitudinal study: Two-fold higher incidence in men. ILSA working group. Italian longitudinal study on aging. *Neurology* **55**, 1358–1363. https://doi.org/10.1212/wnl.55.9.1358 (2000).
5. Dolgacheva, L. P., Zinchenko, V. P. & Goncharov, N. V. Molecular and cellular interactions in pathogenesis of sporadic Parkinson disease. *Int. J. Mol. Sci.* **23** https://doi.org/10.3390/ijms232113043 (2022).
6. de Lau, L. M. & Breteler, M. M. Epidemiology of Parkinson's disease. *Lancet Neurol.* **5**, 525–535. https://doi.org/10.1016/S1474-4422(06)70471-9 (2006).
7. Ascherio, A. & Schwarzschild, M. A. The epidemiology of Parkinson's disease: Risk factors and prevention. *Lancet Neurol.* **15**, 1257–1272. https://doi.org/10.1016/S1474-4422(16)30230-7 (2016).
8. Li, L. Y. et al. Recent research progress on metabolic syndrome and risk of Parkinson's disease. *Rev. Neurosci.* **34**, 719–735. https://doi.org/10.1515/revneuro-2022-0093 (2023).
9. Nam, G. E. et al. Metabolic syndrome and risk of Parkinson disease: A nationwide cohort study. *PLoS Med.* **15**, e1002640. https://doi.org/10.1371/journal.pmed.1002640 (2018).
10. Cheong, J. L. Y., de Pablo-Fernandez, E., Foltynie, T. & Noyce, A. J. The association between type 2 diabetes mellitus and Parkinson's disease. *J. Parkinsons Dis.* **10**, 775–789. https://doi.org/10.3233/JPD-191900 (2020).
11. Park, K. Y., Nam, G. E., Han, K., Park, H. K. & Hwang, H. S. Waist circumference and risk of Parkinson's disease. *NPJ Parkinsons Dis.* **8**, 89. https://doi.org/10.1038/s41531-022-00353-4 (2022).
12. Lu, Y., Jin, X. & Zhao, P. Serum lipids and the pathogenesis of Parkinson's disease: A systematic review and meta-analysis. *Int. J. Clin. Pract.* **75**, e13865. https://doi.org/10.1111/ijcp.13865 (2021).
13. Fu, X. et al. A systematic review and meta-analysis of serum cholesterol and triglyceride levels in patients with Parkinson's disease. *Lipids Health Dis.* **19**, 97. https://doi.org/10.1186/s12944-020-01284-w (2020).
14. Jin, U., Park, S. J. & Park, S. M. Cholesterol metabolism in the brain and its association with Parkinson's disease. *Exp. Neurobiol.* **28**, 554–567. https://doi.org/10.5607/en.2019.28.5.554 (2019).

15. Yoon, S. Y. et al. Initial BMI and weight loss over time predict mortality in Parkinson disease. *J. Am. Med. Dir. Assoc.* **23**, 1719. https://doi.org/10.1016/j.jamda.2022.07.015 (2022). e1711-1719 e1717.
16. Pagano, G. et al. Diabetes mellitus and Parkinson disease. *Neurology* **90**, e1654–e1662. https://doi.org/10.1212/WNL.0000000000005475 (2018).
17. Yoon, S. Y., Shin, J., Kim, Y. W., Chang, J. S. & Won Kim, H. The mortality rate of Parkinson's disease and related comorbidities: A nationwide population-based matched cohort study in Korea. *Age Ageing.* **50**, 1182–1188. https://doi.org/10.1093/ageing/afaa250 (2021).
18. Paley, C. A. & Johnson, M. I. Abdominal obesity and metabolic syndrome: Exercise as medicine? *BMC Sports Sci. Med. Rehabil.* **10**, 7. https://doi.org/10.1186/s13102-018-0097-1 (2018).
19. Mattson, M. P., Pedersen, W. A., Duan, W., Culmsee, C. & Camandola, S. Cellular and molecular mechanisms underlying perturbed energy metabolism and neuronal degeneration in Alzheimer's and Parkinson's diseases. *Ann. N. Y. Acad. Sci.* **893**, 154–175. https://doi.org/10.1111/j.1749-6632.1999.tb07824.x (1999).
20. Perl, D. P., Olanow, C. W. & Calne, D. Alzheimer's disease and Parkinson's disease: Distinct entities or extremes of a spectrum of neurodegeneration? *Ann. Neurol.* **44**, 19–31. https://doi.org/10.1002/ana.410440705 (1998).
21. Rhee, S. Y. et al. Association between glycemic status and the risk of Parkinson disease: A nationwide population-based study. *Diabetes Care.* **43**, 2169–2175. https://doi.org/10.2337/dc19-0760 (2020).
22. Chen, J., Zhang, C., Wu, Y. & Zhang, D. Association between hypertension and the risk of Parkinson's disease: A meta-analysis of analytical studies. *Neuroepidemiology* **52**, 181–192. https://doi.org/10.1159/000496977 (2019).
23. Qiu, C. et al. Association of blood pressure and hypertension with the risk of Parkinson disease: The National FINRISK study. *Hypertension* **57**, 1094–1100. https://doi.org/10.1161/HYPERTENSIONAHA.111.171249 (2011).
24. Simon, K. C., Chen, H., Schwarzschild, M. & Ascherio, A. Hypertension, hypercholesterolemia, diabetes, and risk of Parkinson disease. *Neurology* **69**, 1688–1695. https://doi.org/10.1212/01.wnl.0000271883.45010.8a (2007).
25. Hurh, K., Park, M., Jang, S. I., Park, E. C. & Jang, S. Y. Association between serum lipid levels over time and risk of Parkinson's disease. *Sci. Rep.* **12**, 21020. https://doi.org/10.1038/s41598-022-25180-8 (2022).
26. Ghasemi, R. et al. Brain insulin dysregulation: Implication for neurological and neuropsychiatric disorders. *Mol. Neurobiol.* **47**, 1045–1065. https://doi.org/10.1007/s12035-013-8404-z (2013).
27. Meissner, W. G. et al. Trial of lixisenatide in early Parkinson's disease. *N Engl. J. Med.* **390**, 1176–1185. https://doi.org/10.1056/NEJMoa2312323 (2024).
28. Lovsletten, O. et al. Prevalence of general and abdominal obesity in 2015–2016 and 8-year longitudinal weight and waist circumference changes in adults and elderly: The Tromso study. *BMJ Open.* **10**, e038465. https://doi.org/10.1136/bmjopen-2020-038465 (2020).
29. Dagan, S. S., Segev, S., Novikov, I. & Dankner, R. Waist circumference vs body mass index in association with cardiorespiratory fitness in healthy men and women: A cross sectional analysis of 403 subjects. *Nutr. J.* **12**, 12. https://doi.org/10.1186/1475-2891-12-12 (2013).
30. Craft, S. & Watson, G. S. Insulin and neurodegenerative disease: Shared and specific mechanisms. *Lancet Neurol.* **3**, 169–178. https://doi.org/10.1016/S1474-4422(04)00681-7 (2004).
31. Fulton, S. et al. Leptin regulation of the mesoaccumbens dopamine pathway. *Neuron* **51**, 811–822. https://doi.org/10.1016/j.neuron.2006.09.006 (2006).
32. Zou, X. et al. Role of leptin in mood disorder and neurodegenerative disease. *Front. Neurosci.* **13**, 378. https://doi.org/10.3389/fnins.2019.00378 (2019).
33. Jacobs, E. J. et al. Waist circumference and all-cause mortality in a large US cohort. *Arch. Intern. Med.* **170**, 1293–1301. https://doi.org/10.1001/archinternmed.2010.201 (2010).
34. Koster, A. et al. Waist circumference and mortality. *Am. J. Epidemiol.* **167**, 1465–1475. https://doi.org/10.1093/aje/kwn079 (2008).
35. Hu, H. et al. Waist circumference and all-cause mortality in a middle-aged and elderly Chinese population. *J. Nutr. Health Aging.* **22**, 975–981. https://doi.org/10.1007/s12603-018-1047-z (2018).
36. Iwaki, H. et al. Differences in the presentation and progression of Parkinson's disease by sex. *Mov. Disord.* **36**, 106–117. https://doi.org/10.1002/mds.28312 (2021).
37. Abraham, D. S. et al. Sex differences in Parkinson's disease presentation and progression. *Parkinsonism Relat. Disord.* **69**, 48–54. https://doi.org/10.1016/j.parkreldis.2019.10.019 (2019).
38. Sharma, J. C. & Lewis, A. Weight in Parkinson's disease: Phenotypical significance. *Int. Rev. Neurobiol.* **134**, 891–919. https://doi.org/10.1016/bs.irn.2017.04.011 (2017).
39. Wills, A. M. et al. Predictors of weight loss in early treated Parkinson's disease from the NET-PD LS-1 cohort. *J. Neurol.* **264**, 1746–1753. https://doi.org/10.1007/s00415-017-8562-4 (2017).
40. van der Marck, M. A. et al. Body mass index in Parkinson's disease: A meta-analysis. *Parkinsonism Relat. Disord.* **18**, 263–267. https://doi.org/10.1016/j.parkreldis.2011.10.016 (2012).
41. Wills, A. M. et al. Association between change in body mass index, unified Parkinson's disease rating scale scores, and survival among persons with Parkinson disease: Secondary analysis of longitudinal data from NINDS exploratory trials in Parkinson disease Long-term study 1. *JAMA Neurol.* **73**, 321–328. https://doi.org/10.1001/jamaneurol.2015.4265 (2016).
42. Hill, E. J. et al. Parkinson's disease diagnosis codes are insufficiently accurate for electronic health record research and differ by race. *Parkinsonism Relat. Disord.* **114**, 105764. https://doi.org/10.1016/j.parkreldis.2023.105764 (2023).
43. Kim, B. Y. et al. Korean society for the study of obesity guidelines for the management of obesity in Korea. *J. Obes. Metab. Syndr.* 30, 81–92, (2020). https://doi.org/10.7570/jomes21022 (2021).

Author contributions

Jee Hyun Suh drafted the first version of the manuscript. Seok-Jae Heo was responsible for the statistical analysis. Yong Wook Kim and Sang Chul Lee contributed to the conceptualization of the study. Seo Yeon Yoon supervised the entire research, performed data analysis, and reviewed the manuscript.

Funding information

This work was supported by a National Research Foundation of Korea (NRF) Grant funded by the Korean Government (MSIT) (RS-2024-00337352).

Declarations

Competing interests

The authors declare no competing interests.

Research involving human participants and/or animals

This article does not contain any studies with human participants or animals performed by any of the authors.

Ethical approval

This study was approved by the Institutional Review Board of Yonsei University Health System, Severance Hospital (4-2023-1428).

Informed consent

The nature of this article did not require informed consent.

Additional information

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-025-92624-2.

Correspondence and requests for materials should be addressed to S.Y.Y.

Reprints and permissions information is available at www.nature.com/reprints.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.