Waist circumference and risk of Parkinson’s disease

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Although many studies support the association of obesity with neurodegenerative diseases, such as Parkinson's disease (PD), there are limited data regarding the association between abdominal obesity and PD, with mixed findings. The aim of this study was to examine the association of waist circumference (WC) with the risk of PD incidence. We retrospectively analyzed a large-scale nationwide cohort of 6,925,646 individuals aged ≥40 years who underwent the Korean National Health Screening during 2009. We performed multivariable Cox proportional hazards regression to evaluate the association of WC and abdominal obesity with PD risk and calculated hazard ratios (HRs) with 95% confidence intervals (CIs) of PD incidence. During a median follow-up period of 8.35 years, 33,300 cases of PD developed. PD incidence was positively associated with increases in WC (P for trend < 0.001). The risk of PD incidence tended to elevate as WC increased (P for trend < 0.001), indicating that the adjusted HRs of PD incidence in the highest WC group versus the reference group was 1.16 (95% CI, 1.10–1.23), whereas it was 0.91 (95% CI 0.84–0.98) in the lowest WC group. Individuals with abdominal obesity were significantly associated with an increased PD risk (HR 1.10, 95% CI: 1.07–1.13). These associations persisted even after adjustment for body mass index and stratification by sex. Even among non-obese individuals, abdominal obesity was associated with a higher PD risk (adjusted HR 1.13, 95% CI: 1.09–1.18). Taken together, higher WC and abdominal obesity were associated with increased PD risk. Even in non-obese individuals, abdominal obesity was associated with an increased PD risk.

ARTICLE

INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disease following Alzheimer's disease and affects 6.1 million individuals worldwide, as estimated in 20161. With the increasing aging population, environmental changes, and improved survival of patients with PD, the prevalence of PD is growing fast among all neurologic disorders globally2,3. In South Korea, there has been an upward trend in the age-standardized PD incidence (increasing from 13.6 in 2004 to 26.9 per 100,000 person-years in 2013), with approximately 111,311 individuals affected by PD in 20204.

The precise mechanism of neurodegeneration in PD is not yet fully understood, while aging is known to be the primary risk factor of PD5,6. Several environmental toxins, behavioral factors, and cardiometabolic parameters have also been reported as key factors affecting dopaminergic neuronal cell death at the substantia nigra through oxidative stress, mitochondrial dysfunction, protein misfolding, and some inflammatory mechanisms5–7. Of these, adiposity might be an underlying etiologic factor for age-related neurodegenerative pathologies of PD, since it plays a role in the depletion of striatal dopamine receptor availability8. The deleterious effect of general obesity (measured by body mass index [BMI]) on PD risk has been demonstrated in several epidemiologic studies;5–11 however, other studies reported opposite results or even null associations.12–18 Moreover, studies using anthropometric parameters other than BMI are relatively limited16,19,20.

In light of abdominal obesity, Chen et al. prospectively examined two large cohorts of men and women in the United States (US), and concluded that a greater waist circumference (WC) was associated with future development of PD among never smokers20. Although another US-based cohort study showed null association between WC and PD risk, a European multi-center cohort study in 2019 revealed that female smokers had a 64% increase in the risk of PD development per 10 cm increase in WC16,19. Investigations on the association between central adiposity and PD risk have provided a closer look on the mechanism of PD through the perspective of the effect of adiposity-related inflammation on neurodegeneration. WC is known to be a more reliable parameter for abdominal and visceral accumulation of adipose tissue than BMI. However, most of the previous epidemiologic studies on this issue used European or North American data16,19,20 and some studies relied on self-measured WC data16,19. Although several studies now suggest a potential link between obesity and pathology of neurodegeneration, these few and contradictory findings on WC and PD development prompted us to assess the impact of central adiposity on PD risk. Therefore, we aimed to examine the association between WC, abdominal obesity, and PD risk using the large-scale cohort data of the South Korean population.

RESULTS

Baseline characteristics

The proportions of participants according to the five WC categories were as follows: 2.9% (in group of <70 cm in males, <65 cm in females), 27.3% (70–80 cm in males, 65–75 cm in females), 47.2% (80–90 cm in males, 75–85 cm in females), 19.5% (90–100 cm in males, 85–95 cm in females), and 3.1% (≥100 cm in males, ≥95 cm in females), respectively. Table 1 shows the baseline clinical characteristics of the study population according to WC categories. Individuals in the larger WC levels were older (P < 0.001), and the distributions of income level and lifestyle habits, such as smoking status, alcohol consumption, and physical activity, were significantly different among WC categories (P < 0.001). The mean values of cardiometabolic parameters, such
as BMI, systolic and diastolic blood pressures, total cholesterol, low-density lipoprotein cholesterol, and triglycerides were higher in individuals with greater WC categories \((P < 0.001)\). Individuals in the larger WC categories were more likely to have comorbidities, such as obesity, hypertension, diabetes mellitus, dyslipidemia, and chronic kidney disease \((P < 0.001)\).

**Associations of WC and abdominal obesity with PD incidence**

A total of 33,300 \((0.48\%)\) individuals were diagnosed with PD during the follow-up. Figure 1 shows the Kaplan–Meier curves for incidence probabilities of PD with respect to WC categories and abdominal obesity. The incidence probabilities significantly increased in the higher WC categories in total, male, and female participants \((all \text{ log-rank } P-value < 0.001)\). The plot showed that the cumulative PD incidence increased in total, male, and female participants with abdominal obesity compared with each group without abdominal obesity \((all \text{ log-rank } P-value < 0.001)\). Table 2 presents the adjusted hazard ratios (HRs) \((95\%\text{ confidence intervals [CIs]}\) of PD in five WC categories. Incrementally higher HRs of PD were observed with higher WC categories in the total, male, and female population irrespective of adjustment for confounding variables \((all \text{ } P \text{ for trend} < 0.001)\). In total participants, compared with the second highest level of WC \((70–80 \text{ cm in males and } 65–75 \text{ cm in females})\) as the reference group, the smallest WC group was associated with a 9% lower PD risk \((HR: 0.91, 95\% \text{ CI: 0.84–0.98})\), and the largest WC category was associated with a 16% higher PD risk \((1.16, 95\% \text{ CI: 1.10–1.23})\). In male and female participants, the adjusted HRs of PD in model 2 were 25% \((HR: 1.25, 95\% \text{ CI: 1.14–1.36})\) and 15% \((1.15, 95\% \text{ CI: 1.07–1.23})\) higher in the largest WC group than in the reference groups. These associations remained significant after adjusting for baseline BMI.

Table 3 shows the adjusted HRs \((95\%\text{ CIs})\) of PD in the individuals with abdominal obesity compared with that of those without abdominal obesity. After adjusting for potential confounding variables \((model 2)\), the HRs for PD increased significantly among individuals with abdominal obesity compared with those without in total \((HR: 1.09, 95\% \text{ CI: 1.07–1.13})\), male \((1.11, 95\% \text{ CI: 1.07–1.15})\), and female participants \((1.10, 95\% \text{ CI: 1.07–1.14})\). These associations persisted even after further adjusting for BMI \((model 3)\).

**Subgroup analysis**

Figure 2 shows the associations between abdominal obesity and PD risk in subgroups stratified by age, smoking status, BMI, hypertension, and diabetes mellitus. The associations interacted with age differently between males and females. Positive associations between abdominal obesity and PD risk were stronger among males aged ≥65 years than those aged <65 years, while the associations were stronger among females aged <65 years than those aged ≥65 years. There was a significant interaction with smoking status in the association of abdominal obesity with PD risk in female individuals \((P \text{ for interaction} = 0.023)\), and the association was stronger in those currently smoking than those who were not. Although increased PD risks in abdominal obesity were observed regardless of the presence of general obesity based on BMI ≥25 kg/m², there was no significant interaction with respect to obesity status. The association between abdominal obesity and PD risk was stronger in the total and female population.

### Table 1. Baseline characteristics of the study population.

|                              | N (%) | Age (years) | Current smoker | Alcohol drinker | Regular physical activity | Low income | Body mass index (kg/m²) | Waist circumference (cm) | Systolic BP (mmHg) | Diastolic BP (mmHg) | Fasting glucose (mg/dL) | HDL-C (mg/dL) | eGFR (mL/min/1.73m²) | Obesity | Hypertension | Diabetes mellitus | Dyslipidemia | Chronic kidney disease |
|------------------------------|-------|------------|----------------|----------------|--------------------------|------------|------------------------|------------------------|---------------------|---------------------|------------------------|--------------|-------------------|------|-------------|---------------------|-------------|----------------------|
| <70 in males, <65 in females | 200,827 (2.9) | 51.7 ± 11.1 | 51.9 ± 10.0 | 54.5 ± 10.2 | 57.0 ± 10.6 | 58.5 ± 11.1 | 3,270,108 (47.2) | 63.7 ± 4.0 | 72.6 ± 3.7 | 82.0 ± 3.8 | 90.9 ± 3.5 | 101.1 ± 13.8 | 124.9 ± 15.1 | 124.6 ± 15.3 | 132.3 ± 15.9 | 208,894 ± 124.9 | 144.8 ± 144.9 | 152.8 ± 152.4 | <0.001 |
| 70–80 in males, 65–75 in females | 1,888,818 (27.3) | 52.8 ± 10.0 | 54.1 ± 10.1 | 57.5 ± 10.7 | 60.0 ± 11.1 | 62.5 ± 13.8 | 3,270,108 (47.2) | 63.7 ± 4.0 | 72.6 ± 3.7 | 82.0 ± 3.8 | 90.9 ± 3.5 | 101.1 ± 13.8 | 124.9 ± 15.1 | 124.6 ± 15.3 | 132.3 ± 15.9 | 208,894 ± 124.9 | 144.8 ± 144.9 | 152.8 ± 152.4 | <0.001 |
| 80–90 in males, 75–85 in females | 3,270,108 (47.2) | 53.7 ± 10.5 | 57.5 ± 10.7 | 60.0 ± 11.1 | 62.5 ± 13.8 | 65.0 ± 15.6 | 3,270,108 (47.2) | 63.7 ± 4.0 | 72.6 ± 3.7 | 82.0 ± 3.8 | 90.9 ± 3.5 | 101.1 ± 13.8 | 124.9 ± 15.1 | 124.6 ± 15.3 | 132.3 ± 15.9 | 208,894 ± 124.9 | 144.8 ± 144.9 | 152.8 ± 152.4 | <0.001 |
| 90–100 in males, 85–95 in females | 1,349,990 (19.5) | 54.6 ± 10.9 | 60.5 ± 11.2 | 63.0 ± 11.6 | 65.5 ± 14.1 | 67.5 ± 16.8 | 3,270,108 (47.2) | 63.7 ± 4.0 | 72.6 ± 3.7 | 82.0 ± 3.8 | 90.9 ± 3.5 | 101.1 ± 13.8 | 124.9 ± 15.1 | 124.6 ± 15.3 | 132.3 ± 15.9 | 208,894 ± 124.9 | 144.8 ± 144.9 | 152.8 ± 152.4 | <0.001 |
| ≥100 in males, ≥95 in females | 215,903 (3.1) | 55.5 ± 11.4 | 62.5 ± 12.1 | 65.0 ± 12.6 | 67.5 ± 15.1 | 70.0 ± 17.8 | 3,270,108 (47.2) | 63.7 ± 4.0 | 72.6 ± 3.7 | 82.0 ± 3.8 | 90.9 ± 3.5 | 101.1 ± 13.8 | 124.9 ± 15.1 | 124.6 ± 15.3 | 132.3 ± 15.9 | 208,894 ± 124.9 | 144.8 ± 144.9 | 152.8 ± 152.4 | <0.001 |

**Values are presented as numbers (percentages) or means ± standard deviations.**

*Geometric means (95% confidence intervals). BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate.*

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female populations without hypertension than in those with hypertension ($P$ for interaction < 0.001), and the association was stronger in females without diabetes mellitus than in those with diabetes mellitus ($P$ for interaction = 0.048).

**DISCUSSION**

This large-scale Asian cohort study investigated the association between professionally measured WC and PD risk. In this nationwide cohort, which included 6,925,646 participants aged ≥40 years with 8.35 years of follow-up, we found that higher WC and the presence of abdominal obesity was significantly associated with an elevated PD risk both in males and females. Notably, abdominal obesity was associated with an increased PD risk even in individuals without general obesity. Each subgroup based on age, smoking status, and comorbidities showed consistent results that abdominal obesity was associated with an increased PD risk, although the level of interaction was different according to sex.

Only a few studies have reported the association between WC and PD risk, with inconsistent findings. One recent large-scale European cohort study and another US health professional cohort study revealed a statistically significant positive association between WC and PD risk among women. In accordance with dysregulated insulin signaling, mitochondrial dysfunction in the brain is involved in metabolic disturbance and neurodegeneration. A previous epidemiologic finding showed that metabolic syndrome, a cluster of abdominal obesity and insulin resistance, is associated with the PD risk. In addition, obesity is associated with chronic inflammation states, which is characterized by elevated production of proinflammatory cytokines, thereby leading to oxidative stress and neuronal death. Also, recent evidence on the effect of gut microbiota on α-synucleinopathy or neuroinflammation suggests a dysbiosis-mediated link between adiposity and PD pathogenesis, based on an established association between adiposity and altered gut microbiota.

Besides insulin resistance, accumulated visceral adipose tissue acts as an endocrine organ secreting adipokines, such as leptin and adiponectin, which play an important role in neurodegeneration. Although leptin primarily controls appetite via acting on hypothalamic regions, leptin receptors are expressed in extra-hypothalamic regions, including the substantia nigra. Leptin has a protective effect on dopaminergic neuron degeneration by...
mediating intracellular signaling via the JAK-STAT and ERK/CREB pathways, thus preserving the function of the dopamine system\textsuperscript{29,31,32}. The level of adipokine is inversely associated with central fat distribution\textsuperscript{33}, and individuals with abdominal obesity are suspected to have vulnerability in neuroprotection against 6-hydroxydopamine toxicity, which can accelerate dopaminergic neuron degeneration\textsuperscript{29,31}.

Above all, even normal-weight individuals with abdominal obesity showed an increased PD risk in our results. While normal-weight central obesity and its associated negative health outcomes

| Table 2. Longitudinal associations between waist circumference categories and incident Parkinson's disease. |
|--------|--------|----------------|-----------------|-----------------|------------------|------------------|
| Waist circumference (cm) | N | Event | Person-years | Incidence rate$^a$ | Model 1$^b$ | Model 2$^c$ | Model 3$^d$ |
| Total participants | | | | | | | |
| <70 in males, <65 in females | 200,827 | 623 | 1,619,243 | 0.38 | 0.95 (0.87–1.03) | 0.91 (0.84–0.98) | 0.90 (0.83–0.98) |
| 70–80 in males, 65–75 in females | 1,888,818 | 6267 | 15,457,638 | 0.40 | 1.00 (reference) | 1.00 (reference) | 1.00 (reference) |
| 80–90 in males, 75–85 in females | 3,270,108 | 15,705 | 26,754,898 | 0.58 | 1.44 (1.40–1.49) | 1.10 (1.07–1.13) | 1.11 (1.07–1.14) |
| 90–100 in males, 85–95 in females | 1,349,990 | 1687 | 1,742,378 | 0.96 | 2.39 (2.26–2.52) | 1.16 (1.10–1.23) | 1.19 (1.11–1.27) |
| ≥100 in males, ≥95 in females | 215,903 | 1687 | 1,742,378 | 0.96 | 2.39 (2.26–2.52) | 1.16 (1.10–1.23) | 1.19 (1.11–1.27) |
| P for trend | | | | <0.001 | <0.001 | <0.001 |
| Males | | | | | | | |
| <70 | 76,845 | 318 | 599,779 | 0.53 | 1.12 (0.99–1.25) | 0.86 (0.76–0.96) | 0.84 (0.75–0.95) |
| 70–80 | 777,830 | 2981 | 6,266,622 | 0.47 | 1.00 (reference) | 1.00 (reference) | 1.00 (reference) |
| 80–90 | 1,806,641 | 7883 | 14,675,091 | 0.53 | 1.13 (1.08–1.17) | 1.10 (1.05–1.15) | 1.12 (1.06–1.17) |
| 90–100 | 735,264 | 4039 | 5,947,447 | 0.67 | 1.43 (1.36–1.49) | 1.18 (1.12–1.24) | 1.22 (1.14–1.30) |
| ≥100 | 92,597 | 593 | 740,229 | 0.80 | 1.69 (1.55–1.84) | 1.25 (1.14–1.36) | 1.32 (1.19–1.47) |
| P for trend | | | | <0.001 | <0.001 | <0.001 |
| Females | | | | | | | |
| <65 | 123,982 | 305 | 1,019,464 | 0.29 | 0.84 (0.75–0.94) | 0.95 (0.85–1.07) | 0.95 (0.85–1.07) |
| 65–75 | 1,110,988 | 3286 | 9,191,017 | 0.35 | 1.00 (reference) | 1.00 (reference) | 1.00 (reference) |
| 75–85 | 1,463,467 | 7822 | 12,079,808 | 0.64 | 1.81 (1.74–1.88) | 1.13 (1.08–1.18) | 1.13 (1.08–1.18) |
| 85–95 | 614,726 | 4979 | 5,045,270 | 0.98 | 2.76 (2.64–2.88) | 1.21 (1.16–1.27) | 1.21 (1.15–1.29) |
| ≥95 | 123,306 | 1094 | 1,002,149 | 1.09 | 3.05 (2.85–3.27) | 1.15 (1.07–1.23) | 1.15 (1.05–1.26) |
| P for trend | | | | <0.001 | <0.001 | <0.001 |

$^a$Incidence per 1000 person-years
$^b$Model 1: non-adjusted.
$^c$Model 2: adjusted for age, sex, smoking status, alcohol consumption, physical activity, income, hypertension, diabetes mellitus, dyslipidemia, and chronic kidney disease.
$^d$Model 3: adjusted for body mass index

| Table 3. Longitudinal associations between abdominal obesity and incident Parkinson's disease. |
|--------|--------|----------------|-----------------|-----------------|------------------|------------------|
| Abdominal obesity | N | Event | Person-years | Incidence rate$^a$ | Model 1$^b$ | Model 2$^c$ | Model 3$^d$ |
| Total participants | | | | | | | |
| No | 5,359,753 | 22,595 | 43,831,779 | 0.51 | 1.00 (reference) | 1.00 (reference) | 1.00 (reference) |
| Yes | 1,565,893 | 10,705 | 12,735,095 | 0.84 | 1.63 (1.59–1.67) | 1.10 (1.07–1.13) | 1.09 (1.07–1.12) |
| P-value | | | | <0.001 | <0.001 | <0.001 |
| Males | | | | | | | |
| No | 2,661,316 | 11,182 | 21,541,491 | 0.51 | 1.00 (reference) | 1.00 (reference) | 1.00 (reference) |
| Yes | 827,861 | 4632 | 6,687,677 | 0.69 | 1.33 (1.29–1.38) | 1.11 (1.07–1.15) | 1.10 (1.06–1.14) |
| P-value | | | | <0.001 | <0.001 | <0.001 |
| Females | | | | | | | |
| No | 2,698,437 | 11,413 | 22,290,288 | 0.51 | 1.00 (reference) | 1.00 (reference) | 1.00 (reference) |
| Yes | 738,032 | 6073 | 6,047,418 | 1.00 | 1.96 (1.90–2.02) | 1.10 (1.07–1.14) | 1.09 (1.06–1.13) |
| P-value | | | | <0.001 | <0.001 | <0.001 |

$^a$Incidence per 1000 person-years
$^b$Model 1: non-adjusted.
$^c$Model 2: adjusted for age, sex, smoking status, alcohol consumption, physical activity, income, hypertension, diabetes mellitus, dyslipidemia, and chronic kidney disease.
$^d$Model 3: adjusted for body mass index

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have been widely investigated\textsuperscript{33,34}. Our results imply that neurodegenerative diseases, including PD, can be one of those poor health outcomes of abdominal obesity even in non-obese individuals through the deleterious effects of visceral adipose tissue.

Subgroup analysis in our study showed some interesting results. There was a prominently positive association between abdominal obesity and PD risk in female current smokers and the risk was 1.32-fold higher in female current smokers with abdominal obesity than in those without abdominal obesity. A few studies have
investigated the relationship between central adiposity and PD risk according to smoking status, although the findings differed. Chen et al. reported that the higher WC was associated with an increased PD risk among never smokers of both sexes and female ever smokers. Another evidence has highlighted the smoking status as an effect modifier of PD risk in female smokers; however, Palacios et al. did not observe any significant associations. Current evidence in the genetics of PD may partly explain these contrasting findings, suggesting that ethnicity-specific mutations or variants may have different contributions to the etiologies of PD development. The combination of smoking status and visceral fat distribution might have a different influence on PD risk depending on ethnicity as well as genetic factors. Furthermore, epidemiologic characteristics of the Asian-Pacific region indicate a distinct female predominance of PD prevalence and low smoking rates among females, which could also modify our findings that the PD risk among female smokers with abdominal obesity was more prominent than that among not currently smoking females. This interpretation could be applicable to our findings that males and females showed different interactions with age in the association between abdominal obesity and PD risk. Meanwhile, it is noteworthy that abdominal obesity increased the PD risk irrespective of the presence of diabetes mellitus in our findings, given that diabetes is known as one of risk factors of PD through shared genetic predisposition and pathophysiologic mechanisms. Furthermore, abdominally obese females without diabetes mellitus or hypertension had an increased PD risk compared with abdominally nonobese females without the disease, indicating the possible role of abdominal obesity in PD development in these subgroups.

We acknowledge that some potential limitations should be considered when interpreting the current data. First, a reverse causality might exist between WC and PD risk because of the retrospective cohort design, although we considered a 1-year lag period in identifying PD to overcome this issue. Second, the operational diagnosis of PD based on claim database may cause a possibility of misdiagnosis. However, our diagnostic criteria using the rare and incurable disease registry in the NHIS database could identify PD cases more reliably. Third, the ethnic homogeneity of our data limits the generalizability of our study findings; thus, further studies will be needed in Asian populations with different ethnic backgrounds as well as other races. Fourth, due to the lack of information on the NHIS database, we could not adjust for some confounders affecting WC and PD incidence, such as nutritional intake, including coffee and caffeine intake, education, occupation, and history of exposure to toxic molecules including pesticides. Despite these limitations, our study has several strengths. This study determined the relationship between abdominal obesity and PD risk using the largest cohort database in Asia. The ethnic homogeneity of our study could be viewed as a strength since important differences in genetic factors, etiologies, and management of PD according to the regions are emerging. We confirmed the associations using very large-scale cohort data of South Koreans, which enabled us to consider various confounding variables and detailed subgroup analyses. Another strength of this study was the relatively long-term follow-up period of 8.3 years, which allowed us to more truly examine the causality of abdominal obesity and PD risk. Additionally, we had the WC measured directly by trained health professionals instead of using self-reported data.

In conclusion, in this large, nationwide cohort study comprising South Korean individuals aged ≥40 years, we found a positive association of WC and abdominal obesity with PD risk. WC represents central fat distribution and the level of visceral fat level more accurately than BMI, which makes WC a good indicator of insulin resistance. Our findings suggest that a higher WC and abdominal obesity reflect a PD risk in both obese and non-obese individuals. Of note, our findings can add clarity to the current evidence on the role of abdominal obesity in PD risk and provide valuable insights to risk reduction interventions of PD. Future research is needed to investigate the potential roles of visceral fat-driven adipokines and insulin resistance on PD and neurodegeneration.

METHODS

Data sources

South Korea has launched a single, mandatory universal health insurance system called the National Health Insurance Service (NHIS) in 2000, which almost covers the entire South Korean population. The NHIS in South Korea contains electronic records for sociodemographic variables; health care utilization-related data for all insured people with disease diagnosis data based on the International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM); and mortality data accumulated since 2002. Furthermore, the information on health screening results obtained through the free mandatory National Health Screening Program at least biennially for adults aged ≥19 years are included in the NHIS database. An individual researcher can use the NHIS database under permission granted from the NHIS with the appropriate research proposal for the use of data. The protocol for this study was approved by the NHIS review committee and Institutional Review Board of Korea University Anam Hospital in accordance with the Declaration of Helsinki of the World Medical Association (IRB No. 2019AN0201). The requirement for informed consent was waived as all data used in the analysis was anonymized and de-identified according to strict confidentiality guidelines.

Study participants

Of the 10,585,844 individuals who underwent the national health screening offered by the NHIS between January 1 and December 31 in 2009, we excluded 3,345,043 individuals aged <40 years, 274,452 with missing values for the analysis, and 12,786 diagnosed with PD between 2002 and study enrollment. We further excluded 27,917 individuals diagnosed with PD within 1 year after enrollment. Finally, a total of 6,925,646 individuals were included in the analysis.

Study outcome and follow-up

Newly diagnosed PD was identified on the basis of the ICD-10-CM code for PD (G20), with the PD registration code (V124) in the rare and incurable diseases registry in the NHIS database between January 2010 and December 2018. The rare and incurable disease registry, which also includes PD, has been implemented by the South Korean government since 2006 for copayment reduction by providing financial support to reduce patients’ medical expenses burden. Study participants were monitored until the date of PD diagnosis, date of death, or December 31, 2018, whichever came first. The median follow-up duration for the study endpoint was 8.35 years (interquartile range 8.11–8.60).

Definition of abdominal obesity and WC categories

WC was measured at the narrowest point between the inferior border of the rib cage and iliac crest during minimal respiration. The cutoff point for WC for abdominal obesity in South Koreans was defined as 90 cm for males and 85 cm for females. WC was categorized into five levels as follows: <70, 70–80, 80–90, 90–100, and ≥100 cm in males; <65, 65–75, 75–85, 85–95, ≥95 cm in females.

Other variables

The data for each participant’s smoking status, alcohol consumption, and physical activity were obtained by self-report questionnaire. Smoking status was classified into current smokers or nonsmokers based on the participants’ smoking history. Current smokers were defined as individuals who answered they are currently smoking, and nonsmokers as those who had never smoked or had quit smoking. Participants who had consumed any amount of alcohol were defined as alcohol drinkers. Regular exercise was defined as working out, including either ≥30 min of moderate physical activity at least five times per week or ≥20 min of vigorous physical activity at least three times per week. Income level was dichotomized at the lower 25%, based on employee health insurance premiums reflecting a worker’s salary. BMI was calculated as a participant’s weight in kilograms divided by the square of their height in meters. Obesity was defined as BMI ≥25 kg/m².
m$^2$ based on the World Health Organization recommendations for Asian populations.\textsuperscript{40} Systolic and diastolic blood pressure was measured using a standard mercury sphygmomanometer. Serum glucose, lipid, and creatinine levels were measured after an overnight fast. These health examinations were performed in hospitals certified by the NHS under regular quality control.

The presence of comorbidities, such as hypertension, diabetes mellitus, dyslipidemia, and chronic kidney disease was defined based on the combination of health examination results and ICD-10-CM codes. Hypertension was defined as (a) systolic/diastolic blood pressure $\geq 140/90$ mmHg or (b) having one or more claims for prescription of antihypertensive medications per year under ICD-10-CM codes I10–I13 and I15. Diabetes mellitus was defined as (a) serum fasting glucose level $\geq 126$ mg/dL or (b) having one or more claims for prescription of antidiabetic medication per year under ICD-10-CM code E10–14. Dyslipidemia was defined as (a) serum total cholesterol level $\geq 240$ mg/dL or (b) having one or more claims for prescription of lipid-lowering agents per year under ICD-10-CM code E78. Chronic kidney disease was defined as estimated glomerular filtration rate $< 60$ mL/min/1.73 m$^2$ using the Modification of Diet in Renal Disease equation.\textsuperscript{41}

**Statistical analyses**

Baseline characteristics are presented as means $\pm$ standard deviations for continuous variables and numbers (percentages) for categorical variables according to baseline WC categories. One-way analysis of variance for continuous variables and Pearson’s chi-squared test for categorical variables were used to compare baseline characteristics among the five WC groups. The PD incidence rate was calculated as event number per 1,000 person-years. The cumulative PD incidence according to the five WC categories and the presence or absence of abdominal obesity was plotted using the Kaplan–Meier curves, and the log-rank test was performed to analyze differences among the groups. To investigate the association between WC, abdominal obesity, and PD risk, HRs and 95% CIs values were calculated using the multivariable Cox proportional hazards regression models. Model 1 was not adjusted. Model 2 was adjusted for age, sex, smoking status, alcohol consumption, physical activity, income, hypertension, diabetes mellitus, dyslipidemia, and chronic kidney disease. We further adjusted for baseline BMI in model 3 in addition to the variables adjusted in model 2. These analyses were also performed after stratifying by sex. We performed subgroup analyses by age, smoking status, baseline BMI, hypertension, and diabetes mellitus to investigate the associations between abdominal obesity and PD development in these subgroups. P-value for interaction was calculated using Cox regression analyses. Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). Statistical significance was set at $P < 0.05$.

**DATA AVAILABILITY**

This study was performed using the National Health Insurance System database (https://nhiss.nhis.or.kr/), and the results do not necessarily represent the opinion of the National Health Insurance Corporation. Restrictions apply to the availability of these data, which were used under license for this study.

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AUTHOR CONTRIBUTIONS

K.Y.P.: Writing of the first draft; G.E.N.: Conception, Organization, and Execution of research project, Design of statistical analysis, Review and Critique of the draft; K.H.: Design, Conception and Execution of statistical analysis, Review and Critique of the draft; H.J.P.: Review and Critique of the draft; H.S.H.: Conception of research design, Review and Critique of the draft;

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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