**Supplementary Material**

**Association Between Body Mass Index Changes and All-Cause Mortality in Parkinson’s Disease**

**Supplementary Material 1. Criteria for Parkinson’s disease in the Registration Program for Rare Intractable Diseases**

(1) bradykinesia (a score of at least 2 in the bradykinesia items of the Unified Parkinson’s Disease Rating Scale) with at least one of the following features: muscle rigidity, rest tremor, and postural instability

(2) exclusion of secondary parkinsonism such as stroke, head injury, encephalitis, hypoxic brain injury, and adverse effects of medication

(3) three or more of the following: unilateral onset, rest tremor, disease progression, persistent asymmetry affecting the side of onset, excellent response (70–100%) to levodopa, severe levodopa-induced chorea, levodopa response for 5 years or more, and a clinical course of ten years or more

**Supplementary Table 1. Characteristics of Individuals with Parkinson’s Disease According to Changes in Body Mass Index Status**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Groups classified by changes in body mass index status** | | | | | | | | | |
|  | U 🡪 U | U 🡪 N | U 🡪 O | N 🡪 U | N 🡪 N | N 🡪 O | O 🡪 U | O 🡪 N | O 🡪 O | *p* |
| N | 274 | 187 | 6 | 418 | 10709 | 1339 | 14 | 1793 | 5963 |  |
| Sex (men) | 130 (47.5) | 80 (42.8) | 1 (16.7) | 172 (41.2) | 5364 (50.1) | 601 (44.9) | 3 (21.4) | 803 (44.8) | 2645 (44.4) | <0.0001 |
| Age (y) | 70.4 ± 10.7 | 70.4 ± 10.0 | 74.8 ± 9.6 | 72.9 ± 9.2 | 69.1 ± 9.1 | 68.9 ± 9.0 | 72.9 ± 9.1 | 70.3 ± 8.6 | 68.7 ± 8.5 | <0.0001 |
| Low income level | 54 (19.7) | 33 (17.7) | 1 (16.7) | 65 (15.6) | 1859 (17.4) | 219 (16.4) | 1 (7.1) | 304 (17.0) | 986 (16.5) | 0.7196 |
| Ever smoker | 63 (23.0) | 53 (28.3) | 1 (16.7) | 83 (19.9) | 2646 (24.7) | 327 (24.4) | 1 (7.1) | 365 (20.4) | 1377 (23.1) | 0.0008 |
| Drinker | 35 (12.8) | 16 (8.6) | 0 (0) | 31 (7.4) | 1621 (15.1) | 216 (16.1) | 0 (0) | 208 (11.6) | 913 (15.3) | <0.0001 |
| Physically active | 38 (13.9) | 36 (19.3) | 1(16.7) | 49 (11.7) | 2573 (24.0) | 275 (20.5) | 1 (7.1) | 336 (18.7) | 1309 (22.0) | <0.0001 |
| Height (cm) | 158.5 ± 9.5 | 156.2 ± 9.7 | 153.8 ± 6.8 | 156.6 ± 9.3 | 159.0 ± 9.0 | 157.3 ± 9.1 | 155.8 ± 7.0 | 157.8 ± 9.1 | 158.0 ± 9.1 | <0.0001 |
| Weight (kg) | 42.7 ± 6.1 | 48.9 ± 6.7 | 63.2 ± 7.6 | 43.2 ± 5.8 | 56.3 ± 7.6 | 64.4 ± 7.4 | 40.6 ± 5.1 | 59.1 ± 7.7 | 68.9 ± 9.0 | <0.0001 |
| Body mass index (kg/m2) | 16.9 ± 1.2 | 20.0 ± 1.3 | 26.7 ± 2.5 | 17.5 ± 0.9 | 22.2 ± 1.6 | 26.0 ± 1.1 | 16.7 ± 1.4 | 23.6 ± 1.2 | 27.5 ± 2.1 | <0.0001 |
| Waist circumference (cm) | 67.4 ± 6.5 | 74.4 ±6.8 | 79.8 ± 6.4 | 69.8 ± 6.8 | 79.4 ± 6.8 | 87.4 ± 6.2 | 79.5 ± 12.9 | 83.4 ± 6.6 | 90.7 ± 7.2 | <0.0001 |
| Fasting glucose (mg/dL) | 100.2 ± 24.6 | 101.3 ± 21.3 | 95.3 ± 12.6 | 101.9 ± 28.5 | 103.6 ± 24.5 | 104.3±23.6 | 105.8 ± 45.4 | 106.7 ± 29.1 | 108.3 ± 28.7 | <0.0001 |
| Systolic blood pressure (mmHg) | 121.5 ± 17.3 | 125.4 ± 15.7 | 125.8 ± 13.4 | 121.8± 17.6 | 125.2 ± 15.3 | 127.7 ± 14.6 | 123.4 ± 16.0 | 126.2 ± 15.3 | 129.2 ± 15.3 | <0.0001 |
| Diastolic blood pressure (mmHg) | 74.3 ± 10.1 | 76.4 ± 9.8 | 77.5 ± 6.9 | 74.3 ± 10.6 | 75.7 ± 9.7 | 77.2 ± 9.7 | 77.6 ± 12.8 | 76.1 ± 9.8 | 77.7 ± 9.8 | <0.0001 |
| Total cholesterol (mg/dL) | 180.2 ± 35.4 | 189.3 ± 36.0 | 188.5 ± 32.4 | 174.5 ± 37.3 | 182.8 ± 38.5 | 186.6 ± 40.5 | 179.0 ± 59.3 | 178.9± 39.1 | 183.7 ± 39.8 | <0.0001 |
| eGFR (mL/min/1.73 m2) | 87.9 ± 30.1 | 85.0 ± 23.9 | 77.8 ± 29.3 | 86.0 ± 58.1 | 82.2 ± 40.7 | 79.2 ± 37.4 | 86.0 ± 29.4 | 81.2 ± 52.2 | 79.3 ± 39.1 | <0.0001 |
| Hypertension | 119 (43.4) | 92 (49.2) | 4 (66.7) | 218 (52.2) | 5816 (54.3) | 865 (64.6) | 10 (71.4) | 1201 (67.0) | 4193 (70.3) | <0.0001 |
| Type 2 diabetes | 46 (16.8) | 32 (17.1) | 1 (16.7) | 81 (19.4) | 2370 (22.1) | 294 (22.0) | 3 (21.4) | 545 (30.4) | 1804 (30.3) | <0.0001 |
| Dyslipidemia | 61 (22.3) | 53 (28.3) | 3 (50.0) | 146 (34.9) | 4115 (38.4) | 633 (47.3) | 6 (42.9) | 811 (45.2) | 2996 (50.2) | <0.0001 |
| Chronic kidney disease | 23 (8.4) | 29 (15.5) | 1 (16.7) | 69 (16.5) | 1510 (14.1) | 252 (18.8) | 2 (14.3) | 357 (19.9) | 1061 (17.8) | <0.0001 |

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

eGFR, estimated glomerular filtration rate.

U, Underweight; N, Normal weight or overweight; O, obesity

**Supplementary Table 2. Sensitivity analysis of Mortality Risk in Individuals with Parkinson's Disease According to Nine Groups by Changes in Body Mass Index Status. Laboratory data, blood pressure, and comorbidities were further adjusted.**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Changes in body mass index status | PD (n) | Mortality (n) | Person-years | Mortality rate | aHR (95% CI) |
| Underweight 🡪 Underweight | 274 | 94 | 887 | 106.0 | 2.01 (1.63–2.48) |
| Underweight 🡪 Normal or overweight | 187 | 50 | 628 | 79.6 | 1.50 (1.13–1.99) |
| Underweight 🡪 Obesity | 6 | 0 | 23 | 0.00 |  |
| Normal or overweight 🡪 Underweight | 418 | 172 | 1412 | 121.8 | 1.99 (1.70–2.33) |
| Normal or overweight 🡪 Normal or overweight | 10,709 | 2,020 | 40,358 | 50.1 | 1.00 (reference) |
| Normal or overweight 🡪 Obesity | 1,339 | 197 | 4,938 | 39.9 | 0.82 (0.71–0.96) |
| Obesity 🡪 Underweight | 14 | 7 | 42 | 168.0 | 3.25 (1.54–6.85) |
| Obesity 🡪 Normal or overweight | 1793 | 397 | 6722 | 59.1 | 1.10 (0.99–1.23) |
| Obesity 🡪 Obesity | 5,963 | 852 | 22,775 | 37.4 | 0.80 (0.74–0.87) |
| p value |  |  |  |  | <0.001 |

BMI, body mass index; HR, hazard ratio; CI, confidence interval.

Adjusted for age, sex, income level, lifestyle factors (smoking, drinking, and physical activity), comorbidities (hypertension, type 2 diabetes mellitus, dyslipidemia, chronic kidney disease, metabolic syndrome, myocardial infarction, and stroke), laboratory data (fasting glucose and total cholesterol levels), blood pressure, and disability grade

**Supplementary Table 3. Sensitivity Analysis of Morality Risk in Individuals with Parkinson's Disease According to Weight Change. Laboratory data, blood pressure, and comorbidities were further adjusted.**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Weight change status | PD (n) | Mortality (n) | Person-years | Mortality ratea | aHR (95% CI) |
| Weight loss | 2225 | 576 | 8176 | 70.5 | 1.23 (1.12–1.35) |
| Weight maintenance | 16,946 | 2966 | 64,021 | 46.3 | 1.00 (reference) |
| Weight gain | 1532 | 247 | 5590 | 44.2 | 1.05 (0.92–1.20) |

HR, hazard ratio; CI, confidence interval.

Adjusted for age, sex, income level, lifestyle factors (smoking, drinking, and physical activity), comorbidities (hypertension, type 2 diabetes mellitus, dyslipidemia, chronic kidney disease, metabolic syndrome, myocardial infarction, and stroke), laboratory data (fasting glucose and total cholesterol levels), blood pressure, disability grade, and body mass index

**Supplementary Table 4. Sensitivity analysis of Mortality Risk in Individuals with Parkinson's Disease According to Nine Groups by Changes in Body Mass Index Status. The analysis included 11,254 individuals with a duration of more than two years between the health screening examination and a duration of more than six months between the onset of PD and health screening examination.**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Changes in body mass index status | PD (n) | Mortality (n) | Person-years | Mortality ratea | HR (95% CI) | | | |
| Model 1b | Model 2c | Model 3d |
| Underweight 🡪 Underweight | 154 | 58 | 474 | 122.3 | 2.38 (1.83-3.10) | 2.12 (1.63-2.77) | 2.15 (1.65-2.81) |
| Underweight 🡪 Normal or overweight | 114 | 35 | 386 | 90.6 | 1.74 (1.24-2.44) | 1.64 (1.17-2.29) | 1.54 (1.10-2.15) |
| Underweight 🡪 Obesity | 2 | 0 | 4 | 0 |  |  |  |
| Normal or overweight 🡪 Underweight | 247 | 104 | 819 | 127 | 2.42 (1.98-2.97) | 2.03 (1.66-2.49) | 2.01 (1.64-2.46) |
| Normal or overweight 🡪 Normal or overweight | 5,753 | 1,124 | 21,092 | 53.3 | 1.00 (reference) | 1.00 (reference) | 1.00 (reference) |
| Normal or overweight 🡪 Obesity | 714 | 98 | 2,610 | 37.5 | 0.70 (0.57-0.87) | 0.75 (0.61-0.92) | 0.72 (0.59-0.89) |
| Obesity 🡪 Underweight | 9 | 4 | 30 | 135.3 | 2.59 (0.97-6.91) | 3.84 (1.44-10.28) | 3.37 (1.26-9.03) |
| Obesity 🡪 Normal or overweight | 1031 | 230 | 3794 | 60.6 | 1.13 (0.98-1.31) | 1.13 (0.98-1.30) | 1.09 (0.94-1.26) |
| Obesity 🡪 Obesity | 3,230 | 460 | 12,065 | 38.1 | 0.71 (0.64-0.79) | 0.79 (0.71-0.88) | 0.78 (0.70-0.87) |
| p value |  |  |  |  | <0.0001 | <0.0001 | <0.0001 |

HR, hazard ratio; CI, confidence interval.

aMortality rate is the mortality per 1000 person-year

bModel 1: unadjusted

cModel 2: adjusted for age, sex, income level, and lifestyle factors (smoking, drinking, and physical activity).

dModel 3: adjusted for age, sex, income level, lifestyle factors (smoking, drinking, and physical activity), comorbidities (hypertension, type 2 diabetes, dyslipidemia, and chronic kidney disease), and disability grade

**Supplementary Table 5. Sensitivity Analysis of Morality Risk in Individuals with Parkinson's Disease According to Weight Change. The analysis included 11,254 individuals with a duration of more than two years between the health screening examination and a duration of more than six months between the onset of PD and health screening examination.**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Weight change status | PD (n) | Mortality (n) | Person-years | Mortality ratea | HR (95% CI) | | | |
| Model 1b | Model 2c | Model 3d | Model 4e |
| Weight loss | 1287 | 338 | 4642 | 72.8 | 1.49 (1.33-1.68) | 1.39 (1.24-1.56) | 1.36 (1.20-1.52) | 1.21 (1.08-1.37) |
| Weight maintenance | 9,137 | 1642 | 33,631 | 48.8 | 1.00 (reference) | 1.00 (reference) | 1.00 (reference) | 1.00 (reference) |
| Weight gain | 830 | 133 | 3001 | 44.3 | 0.91 (0.76-1.09) | 0.92 (0.77-1.10) | 0.89 (0.75-1.07) | 0.98 (0.82-1.17) |

HR, hazard ratio; CI, confidence interval.

aMortality rate is the mortality per 1000 person-year

bModel 1: unadjusted

cModel 2: adjusted for age, sex, income, and lifestyle factors (smoking, drinking, and physical activity)

dModel 3: adjusted for age, sex, income, lifestyle factors (smoking, drinking, and physical activity), comorbidities (hypertension, type 2 diabetes, dyslipidemia, and chronic kidney disease), and disability grade

eModel 4: adjusted for age, sex, income, lifestyle factors (smoking, drinking, and physical activity), comorbidities (hypertension, type 2 diabetes, dyslipidemia, and chronic kidney disease), disability grade, and body mass index.

**Supplementary Table 6. Subgroup Analysis of Mortality Risk in Parkinson’s Disease According to Changes in Body Mass Index Status by Sex and Age**

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | | Weight change | | | PD (n) | Mortality (n) | | Person-years | | Mortality ratea | Adjusted hazard ratio (95% CI) | p for interaction |
| Sex | Men | | Underweight 🡪 Underweight | 130 | | | 57 | | 395 | 144.3 | 2.11 (1.62–2.76) | 0.668 |
|  |  | | Underweight 🡪 Normal or overweight | 80 | | | 29 | | 267 | 108.5 | 1.47 (1.01–2.12) |
|  |  | | Underweight 🡪 Obesity | 1 | | | 0 | | 3 | 0.0 | . |
|  |  | | Normal or overweight 🡪 Underweight | 172 | | | 90 | | 524 | 171.9 | 1.99 (1.61–2.47) |
|  |  | | Normal or overweight 🡪 Normal or overweight | 5364 | | | 1278 | | 19334 | 66.1 | 1 (reference) |
|  |  | | Normal or overweight 🡪 Obesity | 601 | | | 112 | | 2100 | 53.3 | 0.81 (0.67–0.99) |
|  |  | | Obesity 🡪 Underweight | 3 | | | 2 | | 5 | 437.4 | 3.66 (0.91–14.71) |
|  |  | | Obesity 🡪 Normal or overweight | 803 | | | 222 | | 2818 | 78.8 | 1.11 (0.96–1.28) |
|  |  | | Obesity 🡪 Obesity | 2645 | | | 511 | | 9741 | 52.5 | 0.86 (0.78–0.96) |
|  | Women | | Underweight 🡪 Underweight | 144 | | | 37 | | 492 | 75.2 | 1.95 (1.40–2.71) |
|  |  | | Underweight 🡪 Normal or overweight | 107 | | | 21 | | 361 | 58.2 | 1.60 (1.04–2.47) |
|  |  | | Underweight 🡪 Obesity | 5 | | | 0 | | 20 | 0.0 | . |
|  |  | | Normal or overweight 🡪 Underweight | 246 | | | 82 | | 889 | 92.3 | 2.08 (1.65–2.61) |
|  |  | | Normal or overweight 🡪 Normal or overweight | 5345 | | | 742 | | 21024 | 35.3 | 1 (reference) |
|  |  | | Normal or overweight 🡪 Obesity | 738 | | | 85 | | 2838 | 30.0 | 0.83 (0.66–1.04) |
|  |  | | Obesity 🡪 Underweight | 11 | | | 5 | | 37 | 134.8 | 3.19 (1.32–7.68) |
|  |  | | Obesity 🡪 Normal or overweight | 990 | | | 175 | | 3905 | 44.8 | 1.08 (0.92–1.28) |
|  |  | | Obesity 🡪 Obesity | 3318 | | | 341 | | 13034 | 26.2 | 0.72 (0.63–0.81) |
| Age | 40–64 | | Underweight 🡪 Underweight | 77 | | | 12 | | 273 | 43.9 | 2.49 (1.40–4.45) | 0.032 |
| (y) |  | | Underweight 🡪 Normal or overweight | 49 | | | 2 | | 199 | 10.1 | 0.61 (0.15–2.44) |
|  |  | | Underweight 🡪 Obesity | 1 | | | 0 | | 7 | 0.0 | . |
|  |  | | Normal or overweight 🡪 Underweight | 76 | | | 8 | | 314 | 25.5 | 1.50 (0.74–3.03) |
|  |  | | Normal or overweight 🡪 Normal or Overweight | 3192 | | | 261 | | 12967 | 20.1 | 1 (reference) |
|  |  | | Normal or overweight 🡪 Obesity | 393 | | | 27 | | 1506 | 17.9 | 0.96 (0.65–1.43) |
|  |  | | Obesity 🡪 Underweight | 4 | | | 2 | | 13 | 153.5 | 6.45 (1.60–26.00) |
|  |  | | Obesity 🡪 Normal or overweight | 442 | | | 51 | | 1803 | 28.3 | 1.24 (0.92–1.68) |
|  |  | | Obesity 🡪 Obesity | 1765 | | | 161 | | 6952 | 23.2 | 1.10 (0.91–.34) |
|  | ≥65 | | Underweight 🡪 Underweight | 197 | | | 82 | | 614 | 133.5 | 1.99 (1.59–2.48) |
|  |  | | Underweight 🡪 Normal or overweight | 138 | | | 48 | | 429 | 111.8 | 1.62 (1.21–2.15) |
|  |  | | Underweight 🡪 Obesity | 5 | | | 0 | | 16 | 0.0 | . |
|  |  | | Normal or overweight 🡪 Underweight | 342 | | | 164 | | 1098 | 149.3 | 2.05 (1.75–2.41) |
|  |  | | Normal or overweight 🡪 Normal or overweight | 7517 | | | 1759 | | 27391 | 64.2 | 1 (reference) |
|  |  | | Normal or overweight 🡪 Obesity | 946 | | | 170 | | 3432 | 49.5 | 0.80 (0.69–0.94) |
|  |  | | Obesity 🡪 Underweight | 10 | | | 5 | | 29 | 174.5 | 2.78 (1.16–6.70) |
|  |  | | Obesity 🡪 Normal or overweight | 1351 | | | 346 | | 4919 | 70.3 | 1.08 (0.96–1.21) |
|  |  | | Obesity 🡪 Obesity | 4198 | | | 691 | | 15823 | 43.7 | 0.75 (0.69–0.82) |

aMortality rate is the mortality per 1000 person-year