Body Mass Index and Risk of Parkinson’s Disease: A Prospective Cohort Study

Giancarlo Logroscino¹, Howard D. Sesso², Ralph S. Paffenbarger, Jr.¹,³, and I-Min Lee¹,²

¹ Department of Epidemiology, Harvard School of Public Health, Boston, MA.
² Division of Preventive Medicine, Department of Medicine, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA.
³ Division of Epidemiology, Stanford University School of Medicine, Stanford, CA.

Received for publication April 4, 2007; accepted for publication June 13, 2007.

High body mass index has been associated with increased risk of several chronic diseases, including cardiovascular disease, and, recently, Alzheimer’s disease. There are few data on the association of body mass index with Parkinson’s disease, and results have been inconsistent. The authors conducted a prospective study among 10,812 men in the Harvard Alumni Health Study, followed from 1988 to 1998 (mean age at baseline: 67.7 years), to test the hypothesis that body mass index is associated with Parkinson’s disease risk. Among 106 incident cases of Parkinson’s disease, body mass index at baseline was not associated with Parkinson’s disease risk (for body mass index <22.5, 22.5–<24.9, and ≥25.0 kg/m²: multivariate relative risks = 1.51 (95% confidence interval: 0.95, 2.40), 1.00 (referent), and 0.86 (95% confidence interval: 0.53, 1.41)). The authors had information on body mass index during late adolescence, when men entered college; this was unrelated to Parkinson’s disease risk as well. Subjects who lost at least 0.5 units of body mass index per decade between college entry and 1988 had a significantly increased Parkinson’s disease risk, compared with men having stable body mass index (multivariate relative risk = 2.60, 95% confidence interval: 1.10, 6.10). The authors conclude that body mass index is unrelated to Parkinson’s disease risk and speculate that the observation of increased risk with body mass index loss since late adolescence may reflect weight loss due to Parkinson’s disease that preceded clinical diagnosis.

body mass index; body weight; cohort studies; obesity; Parkinson disease

Abbreviation: SD, standard deviation.

Obesity is a well-known risk factor for several vascular and metabolic diseases, including diabetes, hypertension, stroke, and myocardial infarction (1, 2). Recent studies have also shown an association between obesity in midlife and cognitive impairment and dementia (3, 4), while larger waist/hip ratio has been linked to brain atrophy (5). However, data regarding an association of high body mass index with risk of Parkinson’s disease are few and contradictory. Parkinson’s disease patients have lower body mass index and weight in clinical series (6) and also when compared with subjects of similar age and gender in a prospective cohort (7). Three prospective cohort studies have examined obesity as a risk factor for Parkinson’s disease. Of these, a recent study from Finland showed an increased risk for subjects who had a high body mass index (8), but the other two studies reported null associations (9, 10). Further, none of these previous studies considered the role of body mass index relatively early in life on the risk of Parkinson’s disease, and weight in early life may be important, having been shown to predict mortality and cardiovascular disease (11–13). We therefore conducted a prospective cohort study to test the hypothesis that body mass index, including assessments from late adolescence as well as middle and older ages, is associated with the risk of Parkinson’s disease.
MATERIALS AND METHODS

Participants

Participants were members of the Harvard Alumni Health Study, a longitudinal cohort study of the predictors of chronic diseases in men who matriculated as undergraduates at Harvard College between 1916 and 1950. Detailed information about the study design has been published previously (14). For the present analyses, 12,805 men who responded to a mailed questionnaire in 1988 asking about demographics, medical history, and health practices were eligible. We excluded men with missing information on weight and/or height on the questionnaire (n = 546), those who reported physician-diagnosed Parkinson’s disease (n = 29), or those who did not provide information on Parkinson’s disease (n = 2). Of the remaining 12,228 men, we successfully followed 10,812 (88.4 percent) through 1998.

Assessment of body mass index

Body weight and height were self-reported on the 1988 questionnaire. Body mass index was calculated (weight (kg)/height (m)^2), and men were categorized into three categories of less than 22.5, 22.5–24.9, and 25.0 or more kg/m^2. According to the World Health Organization classification, we considered men with a body mass index of 25 or more kg/m^2 to be overweight (15). The remaining categories were defined to provide an even distribution of cases across categories.

In addition to body mass index at baseline in 1988, we also had information on measured weight and height at the time these men entered college for 9,903 men (91.6 percent of participants) and on self-reported weight and height via mailed questionnaires in either 1962 or 1966 (1962/1966) for 8,167 (75.5 percent) men.

Assessment of potential confounders

From the 1988 questionnaire, we obtained information at the time of the questionnaire on cigarette smoking (categorized in analyses as never, past, or current smoker; information on the number of cigarettes smoked was available only for the small group of current smokers), tea and coffee intake (for each, categorized in analyses as almost never, ≤1, >1–2, or >2 cups/day; 1 cup = 236.5882 ml), physical activity (assessed as walking, climbing, and participating in sports and recreational activities and categorized as <1,000, 1,000–1,999, 2,000–2,999, or ≥3,000 kcal/week), and whether men had been diagnosed by their physicians to have cardiovascular disease and cancer (no or yes).

Ascertainment of Parkinson’s disease

On a health questionnaire mailed in 1993, we asked men about physician-diagnosed Parkinson’s disease. In addition, men were followed for mortality through 1998, and death certificates were obtained. Using both methods, we identified 106 men with Parkinson’s disease during follow-up. Self-reported Parkinson’s disease in this cohort is reasonably valid: In a previous validation study, self-reported diagnosis of Parkinson’s disease was confirmed in all cases by the treating physician (70.1 percent of physicians participated in the validation study) (16).

Statistical analysis

We used Cox proportional hazard models to estimate the relative risks and 95 percent confidence intervals of Parkinson’s disease according to categories of body mass index in 1988 and at college entry. Initial models adjusted for age, while multivariate models also adjusted for smoking, tea and coffee consumption, and physical activity. Additionally, we adjusted for previous diagnosis of cardiovascular disease or cancer, since these chronic diseases may have altered men’s body mass index. We repeated these analyses, excluding the first 4 years to minimize bias from weight loss preceding a clinical diagnosis, since a recent prospective study showed that weight loss may precede the diagnosis of Parkinson’s disease by some 2–4 years (7). We then examined the association of change in body mass index between college entry and 1962/1966. The rationale for choosing this time period is that, first, we were interested in change in body mass index between late adolescence and middle age, and, second, body mass index in 1962/1966 was unlikely to be affected by weight change resulting from preclinical Parkinson’s disease diagnosed after 1988. We further examined the association of change in body mass index between college entry and 1988. In analyses of change in body mass index, we further adjusted for body mass index at college entry, since men losing weight after college entry are more likely to be heavier initially, and men gaining weight more likely to be leaner initially.

RESULTS

Table 1 shows the baseline characteristics of men according to their body mass index. The mean age of all 10,812 men in 1988 was 67.7 (standard deviation (SD): 8.1) years. Their mean body mass index was 24.7 (SD: 3.0) kg/m^2, and 42.0 percent were overweight (body mass index: ≥25 kg/m^2). Overweight men were less likely to smoke or drink tea but more likely to drink coffee. There was a U-shaped relation with physical activity, with the leanest and heaviest men being less active than men in the middle body mass index category. Lean men also had a higher prevalence of cardiovascular disease and cancer at baseline; this is likely a reflection of the disease processes; that is, men with cardiovascular disease may have been advised to lose weight, while men with cancer may have lost weight because of the disease.

During the 63,557 person-years of follow-up after the return of the 1988 questionnaire until 1998, we identified 106 cases of Parkinson’s disease. The mean duration to onset of Parkinson’s disease after 1988 was 5.2 (SD: 2.2) years. Increased body mass index levels at college entry and in 1988 were not associated with increased risk of Parkinson’s disease (table 2). Our conclusions did not change when we excluded the first 4 years of follow-up after 1988 (data not shown).

We next examined the association of weight change from college entry to 1962/1966 with the risk of developing
TABLE 1. Baseline characteristics of men in 1988 according to body mass index, Harvard Alumni Health Study

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Body mass index (kg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;22.5</td>
</tr>
<tr>
<td></td>
<td>22.5–24.9</td>
</tr>
<tr>
<td></td>
<td>≥25.0</td>
</tr>
<tr>
<td>(n = 2,374)</td>
<td>(n = 3,893)</td>
</tr>
<tr>
<td>Age (years) (mean (SD*))†</td>
<td>70.0 (8.8)</td>
</tr>
<tr>
<td>Cigarette smoking (%)‡</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>39.9</td>
</tr>
<tr>
<td>Former</td>
<td>50.5</td>
</tr>
<tr>
<td>Current</td>
<td>9.7</td>
</tr>
<tr>
<td>Tea consumption (%)†</td>
<td></td>
</tr>
<tr>
<td>Almost never</td>
<td>48.9</td>
</tr>
<tr>
<td>≤1 cup/day</td>
<td>27.7</td>
</tr>
<tr>
<td>&gt;1–2 cups/day</td>
<td>18.9</td>
</tr>
<tr>
<td>&gt;2 cups/day</td>
<td>4.5</td>
</tr>
<tr>
<td>Coffee consumption (%)‡</td>
<td></td>
</tr>
<tr>
<td>Almost never</td>
<td>33.4</td>
</tr>
<tr>
<td>≤1 cup/day</td>
<td>15.0</td>
</tr>
<tr>
<td>&gt;1–2 cups/day</td>
<td>36.9</td>
</tr>
<tr>
<td>&gt;2 cups/day</td>
<td>14.7</td>
</tr>
<tr>
<td>Physical activity (kcal/week) (%)†</td>
<td></td>
</tr>
<tr>
<td>&lt;1,000</td>
<td>34.5</td>
</tr>
<tr>
<td>1,000–1,999</td>
<td>22.3</td>
</tr>
<tr>
<td>2,000–2,999</td>
<td>16.2</td>
</tr>
<tr>
<td>≥3,000</td>
<td>27.1</td>
</tr>
<tr>
<td>History of cardiovascular disease or cancer (%)†</td>
<td></td>
</tr>
<tr>
<td></td>
<td>30.7</td>
</tr>
</tbody>
</table>

* SD, standard deviation.
† p < 0.05 for comparison among groups.
‡ One cup = 236.5882 ml.

Parkinson’s disease (table 2). There was no significant association between either weight loss or weight gain with risk of Parkinson’s disease developing between 1988 and 1998. Finally, we examined the association of weight change between college entry and 1988 with Parkinson’s disease diagnosed after 1988. Weight loss was significantly related to a higher risk of Parkinson’s disease: Men losing more than 0.5 units of body mass index (approximately 1.6 kg for a 1.8-m-tall person) per decade had a multivariate relative risk of 2.60 (95 percent confidence interval: 1.10, 6.10).

DISCUSSION

In this prospective cohort study, no association was found between body mass index measured in adolescence or later in life and risk of Parkinson’s disease. Similarly, no association was found between change in body mass index occurring between adolescence and middle life and Parkinson’s disease risk. However, weight loss from late adolescence to a time immediately preceding the diagnosis of Parkinson’s disease was associated with more than a doubling of risk for Parkinson’s disease. We speculate that this observation of increased risk may reflect weight loss resulting from Parkinson’s disease, which preceded a clinical diagnosis. This observation was based on a small number of incident cases, leading to an imprecise estimate of the relative risk with wide confidence intervals.

Weight loss is a common manifestation among the elderly. In addition, Parkinson’s disease patients lose weight during the course of disease and are generally thinner compared with healthy controls (6, 17). In the present analyses, the mean duration to Parkinson’s disease diagnosis after body mass index assessment in 1988 was 5.2 years. This suggests that a body mass index decline occurred at least 5 years prior to clinical diagnosis of Parkinson’s disease. Consistent with these data, a recent prospective study showed that weight loss may precede the diagnosis of Parkinson’s disease by some 2–4 years (7).

The observed decline in body mass index may stem from subclinical effects of the disease, such as change in dietary habits, or early motor signs including initial rigidity and bradykinesia. Alternatively, it may be part of the constellation of primary nonmotor symptoms, such as constipation and sleep disorders, that are now being considered as possible early symptoms that can precede the diagnosis by many years (7, 18–20). Neurodegenerative pathologic changes due to loss of dopaminergic neurons may induce an altered pattern of food intake. Dopamine acts locally as a potent inhibitor of feeding in several areas of the central nervous system, and Parkinson’s disease patients characteristically have increased energy intake (21). This apparently precedes disease onset; therefore, the decline in body mass index cannot be explained by reduced energy intake (7). However, a negative balance due to increased energy requirements because of subtle motor symptoms, even in the presence of higher energy intake, may result in body mass index loss. Other areas of the brain may be involved in these processes as well. Hippocampus atrophy, which has been associated with loss of weight in Alzheimer’s disease (22), has been recently described as present in nondemented Parkinson’s disease patients (23) and, therefore, may be also responsible for weight loss in Parkinson’s disease patients.

High body mass index in late adolescence and early adulthood has been extensively investigated as a risk factor for all-cause mortality and cardiovascular disease; this has been shown to be positively related to risk of both cardiovascular disease and death occurring much later in life (11–13). Similarly, we hypothesized that a high body mass index early in life may be relevant for late-onset neurodegeneration in Parkinson’s disease. To our knowledge, this is the first study to investigate the role of body mass index relatively early in life (body mass index during college entry was typically measured at age 18 years for participants) and risk of Parkinson’s disease. The present null results on the role of body mass index, including during late adolescence, and risk of Parkinson’s disease are consistent with those from two other cohort studies that have explored the association between obesity and Parkinson’s disease risk (9, 10), but in contrast to a Finnish study (8). Obese subjects, because of the medical attention they receive due to other medical...
conditions such as cardiovascular diseases, may be more likely to be diagnosed with Parkinson’s disease. This may be particularly relevant in Finland where the national medical system may increase the likelihood of close medical surveillance for persons (such as those obese) at increased risk for chronic diseases. This ascertainment bias may partly explain the findings in the Finnish cohort; however, further studies are needed to resolve this inconsistency.

Other measures of adiposity in relation to Parkinson’s disease risk have been examined in prospective studies. Among Japanese Americans living in Hawaii, a high triceps skinfold thickness, a measure of peripheral adiposity, in midlife increased the risk of Parkinson’s disease threefold over a 30-year period (9). In another large cohort study of US men and women, extreme quintiles of waist circumference and waist/hip ratio in midlife doubled the risk of Parkinson’s disease, but only among never smokers (10). We did not have these measurements available in our cohort and were not able to examine these other measures of adiposity.

Some limitations should be considered in the interpretation of our results. In this study, Parkinson’s disease was self-reported or determined from death certificates. We believe our ascertainment of Parkinson’s disease to be valid, as a previous validation study found that all self-reported, physician-diagnosed Parkinson’s disease was confirmed by the treating physician (70.1 percent participation rate by physicians) (16), suggesting that Parkinson’s disease misdiagnosis in this cohort was probably minimal. Furthermore,
in a population-based study, about 80 percent of subjects who self-reported Parkinson’s disease had an insurance claim with a Parkinson’s disease diagnosis, filed by the treating physician (24). As for weight and height, these were measured during college entry, but subsequent measures were self-reported. However, self-reported weight has been shown to correlate highly with measured weight among well-educated male subjects (r = 0.97) (25). We were unable to examine very high levels of body mass index in this study, since few men had body mass indexes in excess of 30 kg/m². Although we were able to control for several potential confounders, it is possible that other unmeasured factors may have confounded the findings. As in many published studies of incident Parkinson’s disease, our sample size was relatively small, and therefore the power to detect positive associations was limited. Finally, this is a homogeneous cohort of subjects with high education and socioeconomic status. Although this may limit the generalizability of our findings, it also may minimize unmeasured confounding. Strengths of the present study include repeated assessments of body mass index, detailed information on relevant potential confounders such as smoking and caffeine use, and a high follow-up rate.

In conclusion, this prospective study did not show an association between body mass index and risk of Parkinson’s disease. However, weight loss between adolescence and later life (on average, 5 years proximate to the diagnosis of Parkinson’s disease) predicted a higher risk of Parkinson’s disease. We speculate that this increased risk may reflect weight loss due to Parkinson’s disease, which preceded the clinical diagnosis.

ACKNOWLEDGMENTS

This research was supported by grant HL077548 from the National Heart, Lung, and Blood Institute.

The authors are grateful to Sarah E. Freeman, Rita W. Leung, Doris C. Rosoff, and Alvin L. Wing for their help with the College Alumni Health Study.

This is report LXXXIX in a series on chronic disease in former college students.

Conflict of interest: none declared.

REFERENCES