Published in final edited form as:
Mov Disord. 2011 October ; 26(12): 2253–2259. doi:10.1002/mds.23855.

Obesity, Diabetes and Risk of Parkinson Disease

Natalia Palacios, ScD[1], **Xiang Gao, MD PhD**[1,5], **Marjorie L. McCullough, ScD**[2], **Eric J. Jacobs, PhD**[2], **Alpa V. Patel, PhD**[2], **Tinisha Mayo, MPH**[2], **Michael A. Schwarzschild, MD, PhD**[3], and **Alberto Ascherio, MD, DPH**[1,4,5]

[1]Dept. of Nutrition, Harvard School of Public Health 655 Huntington Ave., Boston, MA 02115

[2]Epidemiology Research Program, American Cancer Society, 250 Williams St., Atlanta, GA 30303

[3]Massachusetts General Hospital, Boston, MA, 02114

[4]Dept. of Epidemiology, Harvard School of Public Health 677 Huntington Ave., Boston, MA 02115

[5]Channing Laboratory, Department of Medicine, Brigham and Women's Hospital, and Harvard Medical School, Boston, MA 02115

Abstract

Background and Objective—To investigate whether obesity and diabetes are related to risk of Parkinson disease (PD).

Methods—We prospectively followed 147,096 participants in the Cancer Prevention Study II Nutrition Cohort from 1992 to 2005. Participants provided information on anthropometric variables and medical history at baseline, and on waist circumference in 1997. Incident cases of PD (n = 656) were confirmed by treating neurologists and medical record review. Relative risks (RR) were estimated using proportional hazards models, adjusting for age, gender, smoking and other risk factors.

Results—Neither BMI nor waist circumference significantly predicted PD risk. The RR comparing individuals with a baseline BMI of ≥ 30 to those with a BMI < 23 was 1.00 (95% CI: 0.75, 1.34; p-trend: 0.79), and that comparing individuals with a waist circumference in the top category (>=40.3 inches in men and >=35 inches in women) to those in the bottom category (<34.5 inches in men and <28 inches in women) was 1.35 (95% CI 0.95, 1.93; p-trend 0.08).

Corresponding Author: Natalia Palacios, ScD, Dept. of Nutrition, Harvard School of Public Health 655 Huntington Ave., Boston, MA 02115 phone and fax: (617)304-4254 (phone) palacios@hsph.harvard.edu.

AUTHOR ROLES

Natalia Palacios: Performed the data analysis, wrote the first draft of the manuscript and edited subsequent drafts
Xiang Gao: Acquisition of data, critical revision of manuscript
Marji McCullough: Acquisition of data, critical revision of manuscript
Eric Jacobs: Analysis and interpretation of data, critical revision of manuscript.
Alpa Patel: Acquisition of data, critical revision of manuscript
Tinisha Mayo: Analysis and interpretation of data, critical revision of manuscript, administrative and clerical support.
Michael Schwarzschild: Acquisition of data, critical revision of the manuscript.
Dr. Alberto Ascherio: Conception and design, acquisition of data, analysis and interpretation of data, critical revision of the manuscript, obtaining funding, statistical expertise.

FINANCIAL DISCLOSURES Disclosures Related to Manuscript (Full Disclosure will be submitted in case of acceptance or upon request by the editor).
Marji McCullough has nothing to disclose
Eric Jacobs has nothing to disclose
Alpa Patel has nothing to disclose
Tinisha Mayo has nothing to disclose
Michael Schwarzschild has nothing to disclose

The study is NOT industry-sponsored.

History of diabetes was not significantly associated with PD risk (combined RR = 0.88; 95 % CI: 0.62, 1.25; p-heterogeneity = 0.96). In addition, neither BMI at age 18, nor changes in weight between age 18 and baseline were significantly associated with PD risk. The results did not differ significantly by gender

Conclusion—Our results do not provide evidence for a relationship between BMI, weight change, waist circumference or baseline diabetes and risk of PD.

INTRODUCTION

Obesity, defined as a body mass index (BMI) over 30, has been established as a risk factor for a variety of diseases, including several cancers[1, 2] heart disease[3, 4] type II diabetes[5] and Alzheimer's disease.[6] Dopamine may play an important role in both obesity (e.g., by regulating energy intake[7, 8]) and PD in which there is a loss of dopaminergic neurons and thus lower dopamine activity in the hypothalamus.[9, 10]

In two prospective studies, BMI and other anthropometric measures were related to increased risk of PD. In a Finnish cohort, risk of PD was two-fold higher among men with BMI over 30 as compared to those with BMI under 23; a 70% higher risk was observed in an analogous comparison in women.[11] Among men of Japanese ancestry in Hawaii, PD risk increased with increasing triceps skinfold thickness[12] , although not with BMI. In contrast, in two other large prospective cohorts, the Nurses Health Study (NHS) and the Health Professionals Follow-up Study (HPFS), obesity was not related to risk of PD.[13] A similar null result was found for obesity and self-reported PD in the Harvard Alumni Study.[14]

Type II diabetes is a growing public health problem.[15, 16] There is some evidence of a high prevalence of insulin resistance in Parkinson patients, although the mechanism is still debated.[17] Obesity is a strong predictor of type II diabetes.[5] In models adjusting for BMI, baseline diabetes has been associated with an over 80% increase in risk of PD in a prospective Finnish cohort of men and women.[18] However, in the NHS and the HPFS, neither men nor women with diabetes at baseline were at altered risk of PD.[19] In a third prospective study, a modest positive correlation was found between self-reported diabetes and self-reported PD.[20]

We therefore examined prospectively whether anthropometric factors, including BMI at baseline and in young adulthood, weight change in adulthood, waist circumference, and location of weight gain, and a history of diabetes was associated with risk of PD in the American Cancer Society CPS II Nutrition Cohort.

METHODS

Study population

The CPS-II Nutrition cohort (Nutrition Cohort) was established in 1992 and is a subgroup of the original 1982 CPS II mortality cohort. The Nutrition Cohort includes 184,190 participants (86,404 men and 97,786 women) from 21 U.S. states, who reported their medical histories, lifestyle characteristics, and dietary habits in response to a mailed baseline (1992-1993) questionnaire.[21] About 97% of the participants reported their race/ethnicity as white. Participants had also reported their medical, lifestyle and dietary intake information on a questionnaire during their original enrollment in 1982. In 1997, the participants responded to a follow-up questionnaire that was very similar to the baseline 1992 questionnaire, but also included additional questions, in particular asking participants to measure and report their waist circumference in inches. As part of cohort follow-up, in 2001, participants were asked to report if they had ever been diagnosed with PD, as described

previously.[22] We included in this study the 147,096 (63,303 men and 79,949 women) cohort participants who returned one or more of the 2001, 2003 or 2005 questionnaires and had no symptoms nor a diagnosis of PD at study baseline in 1992.

Additional exclusions were made in each analysis to account for those missing the exposure variable of interest (BMI, diabetes and others). This study was approved by the Human Subjects Committee at the Harvard School of Public Health (HSPH) and the Institutional Review Board (IRB) at Emory University.

Assessment of BMI, body composition and diabetes

BMI (weight in kg/height in m^2) at baseline was calculated using self-reported weight (in 1992) and height (reported in 1982) and categorized into five categories as follows: 18.5-23 (ref), 23-24.9, 25-26.9, 27-29.9 and >=30. Participants with a BMI of lower than 18.5 in 1992 were excluded from these analyses (n = 9) because the weight of these participants may be low due to undiagnosed PD. Because younger individuals tend to be leaner, we categorized BMI at age 18 (using recalled weight at age 18 reported in 1992 and height reported in 1982) in the following way: <20 (ref), 20-22.4, 22.5-24.9, 25-26.9 and >=27. The same category cutoffs for BMI at baseline and BMI at age 18 were used for men as for women.

We categorized weight change in pounds between age 18 and 1992 in the following five a priori defined categories (participants with a 5+ lb weight loss were excluded): weight maintainers (ref) [defined as <5 lb of weight loss, no change in weight or <5 lb weight gain], and gain of 5-14.9 lb, 15-24.9 lb, 25-44.9 lb, ≥ 45lb. Additionally, participants were asked "When you gain weight, where on your body do you mainly add the weight: chest and shoulders, waist, hips and thighs, other part of the body, equally all over, or don't gain weight?" Central weight gain was defined as reported weight gain in the chest and shoulders or waist, and peripheral weight gain was defined as reported weight gain in hips and thighs or equally all over.[23] On the 1997 questionnaire, participants were asked to measure their waist just above the navel with a tape measure while standing (without wearing bulky clothing) and to record it to the nearest ¼ inch. Waist circumference was categorized in the following a priori defined categories based on a previous publication on adiposity and risk of PD: (men: <34.5, 34.5-36.2, 36.3-37.9, 38.0-40.2 and >=40.3 inches; women: <28.0, 28.0-29.9, 36.3-37.9, 38.0-40.2, >=40.3 inches).[13]

Parkinson disease case ascertainment

The initial procedures for case ascertainment were based on those in our prior studies on PD.[24] We contacted all CPS-II Nutrition Cohort participants who reported a diagnosis of PD on the 2001, 2003 and 2005 questionnaires and requested permission to contact their treating neurologists and obtain copies of their medical records. The treating neurologists, or internists, who were contacted if the neurologists did not respond, were asked to respond to a diagnostic questionnaire or to mail us a copy of the participant's medical record. The questionnaire included questions regarding cardinal signs of PD (rest tremor, rigidity, bradykinesia, and postural instability), response to levodopa treatment, and the presence of other symptoms or features to support a diagnosis of PD or suggest an alternative diagnosis. Cases were labeled as confirmed for the purpose of this study if the PD diagnosis was considered definite or probable by the treating neurologist or internist, or if the medical record indicated a final diagnosis of PD made by a neurologist or evidence at a neurological exam of at least two of the four cardinal signs (with one being rest tremor or bradykinesia), a progressive course, and the absence of unresponsiveness to levodopa or other features suggesting an alternative diagnosis. Similar procedures were implemented to confirm PD cases reported in the 2003 and 2005 follow-up questionnaires, except that copies of the

medical records were requested for all cases and were reviewed by a movement disorder specialist (M.A.S.).

Within the cohort, 1810 participants self-reported PD in 2001, 2003 or 2005 and returned a follow-up consent form. Of these, 1055 consented to have their medical records reviewed, 246 confirmed that they have PD but did not consent to medical record review, 328 denied having PD, 54 refused to participate and 127 had died. A diagnosis of PD was confirmed in 877 cases. Of the confirmed cases, 220 were excluded because their symptoms onset occurred before the baseline survey and one was excluded due to missing all three of the 2001, 2003 and 2005 surveys. Of the 656 incident cases included in this analysis, 75% were confirmed by the treating neurologists or movement disorders specialists, 13% by the review of neurological medical records, 6% by the treating internists or family physicians and 6% by other physicians. The proportion of cases confirmed did not vary from that not confirmed by BMI at baseline, BMI at age 18, weight change, area of weight gain, waist circumference or the self-report of diabetes. In a sensitivity analysis, we included self-reported cases who met the above criteria and had reported the onset of PD during the study follow-up period (164 men and 82 women).

Statistical analyses

All anthropometric variables were analyzed as categorical variables, with the median value in each category used to create a continuous variable for linear trend tests. This was done to minimize the potential effects of extreme values on regression analysis and to allow for nonlinear associations. Study follow-up lasted from the date of return of the 1992 questionnaire to the earlier of date of return of the latest complete questionnaire (August 31, 2001, 2003 or 2005 respectively), date of onset of the first symptoms of PD or date of death, except in analyses of waist circumference (collected in 1997) where follow-up lasted from the date of return of the 1997 questionnaire to the earlier of either the date of return of the latest complete questionnaire (August 31, 2001, 2003 or 2005), date of death, or date of onset of the first PD symptoms. Multivariate relative risks were calculated using Cox proportional hazards models, with adjustment for 1) age in months and smoking in quintiles of pack years and 2) age in months and smoking in quintiles of pack years, alcohol intake, caffeine intake, caloric intake, dairy intake, pesticide exposure, education and physical activity. In analysis of diabetes, BMI was also entered into the model as a covariate. We calculated 95 percent confidence (95% CI) intervals for all relative risks and all p values were two-tailed ($\alpha = 0.05$). Gender specific and combined analyses are presented. The combined estimate was calculated by weighting the gender-specific log relative risks by the inverse of their variances using a random-effects model.[25]

RESULTS

We documented a total of 420 male and 236 female cases during follow-up in this cohort. The age range at baseline (in 1992 when BMI was assessed) for the cohort was 63.6 years old in men and 62.0 years old in women. The mean age at onset and range for the PD cases was 71.9 years (range: 56.9 – 93.9 years) in men and 71.2 years (range: 55.0 to 88.0 years) in women. The mean time from baseline to PD diagnosis and range was 6.3 years (range: 0.25 – 12.7) years in men and 6.4 years (range: 0.25-12.7) in women. Table 1S in the appendix describes the baseline characteristics of the population.

No significantly altered risk of PD was observed in analyses of BMI at baseline (in 1992) (Table 1). Using BMI 18.5-23 as the reference group, the multivariate-adjusted relative risk for a BMI of 30 or more was 1.00 (95 percent confidence interval (CI): 0.75, 1.34; p-trend: 0.79).

BMI in early adulthood (age 18) did not predict later risk of PD (Table 1); the combined multivariate relative risk comparing the top category of BMI (≥27) to the bottom category (<20) was 1.15 (95% CI: 0.76, 1.73; p-trend: 0.23). Men who gained a significant amount of weight between age 18 and study baseline were at a slightly lower risk of PD compared to those who gained little or no weight or lost weight (Table 1). The relative risk comparing those who had gained 45 pounds or more (top category) between age 18 and study baseline in 1992 to those who had gained less than 5 pounds (bottom category) was 0.54 (95% CI: 0.35, 0.85, p –trend: 0.34) in men and 0.62 (95% CI: 0.32, 1.21; p-trend: 0.05) in women. The association with weight gain could have been caused by recent weight loss or absence of weight gain due to undiagnosed PD. To examine the possibility that this effect was due to a loss of weight among women with undiagnosed PD, we conducted a sensitivity analysis excluding the first five years of follow-up. In this analysis, the RR comparing the women in the top category of weight gain to the lowest category was 0.72 (95% CI: 0.36, 1.42, p-trend: 0.35).

Waist circumference reported in 1997 did not appear to predict risk of PD in men or in women (Table 2); the RR comparing the highest to the lowest category in the multivariate combined analyses was 1.35 (95% CI: 0.95, 1.93; p-trend: 0.08) (Table 2).

A diagnosis of diabetes at baseline in 1992 was not significantly related to PD risk. The multivariate combined RR of PD among those with diabetes at baseline was 0.88 (95% 0.62, 1.25; p-trend: 0.40).

Central weight gain, defined as a self-reported tendency to gain weight predominantly in the chest and shoulders or waist rather than in the hips and thighs or ‘equally all over’, was not significantly associated with PD risk. Men and women who reported a tendency for central weight gain had a combined RR of 0.89 (95% CI: 0.75, 1.06; p = 0.20) of developing PD during follow-up.

Because of the strong inverse relationship between smoking and PD risk, we also conducted analyses stratified by smoking history (never vs. ever smoker at baseline). We did not observe any significant interactions with smoking and none of the results differed significantly by smoking status (data not shown).

To account for possible influence of undiagnosed PD on our results, we conducted sensitivity analyses excluding the first five years of follow-up. Other than the loss of significance in the effect of weight change on risk of PD in women mentioned above, the results were not significantly altered.

While the primary analyses were conducted among participants for whom we were able to obtain medical records, around 20% of PD cases (164 men and 82 women) in our study reported a diagnosis of PD but did not provide consent to contact their treating neurologist or internist. We repeated the analyses including all participants who reported PD, whether or not they provided consent to contact their neurologist. The results did not materially change by including these additional participants. In these analyses, the association with waist circumference in men reached statistical significant (p-trend: 0.04).

Because weight gain and loss are strongly related to age, we conducted additional sensitivity analyses stratifying on age at baseline dichotomized at 60 years of age. In our cohort, 125 PD cases (80 male and 45 female) were 60 years old or younger at baseline in 1992 and 531 PD cases (340 male and 191 female) were over 60 years old at baseline. We observed a significant interaction of BMI at age 18 with age at baseline (p-int = 0.009) in women. Women under 60 at baseline, with higher BMI at age 18 were at an increased risk of PD (p-trend: 0.004); no relation was found in women 60 or older at baseline or in men of either

age. No effect of BMI in 1992 on risk of PD was observed in either age category in neither men nor women. No interactions with age at baseline were observed for weight change, tendency for central weight gain, waist circumference or diabetes at baseline in men or women.

DISCUSSION

In this large prospective cohort of US men and women, we did not find significantly altered risk of PD when examining BMI, weight change, tendency for central weight gain or baseline diabetes. Among women, PD risk decreased with increasing weight gain after age 18, but this RR was only marginally significant and was attenuated in sensitivity analyses.

The advantages of this study include its large size, longitudinal design with a large number of confirmed incident PD cases, and the thoroughly collected prospective data on exposure variables as well as on potential confounders. We were able to analyze not only BMI and history of diabetes, but also a number of anthropometric factors, such as waist circumference, change in weight, body area where weight is gained, as well as BMI in young adulthood, providing for a comprehensive analysis of the relationship between adiposity and risk of PD. The diagnosis of PD was based on medical records obtained from the patient's neurologist and reports from treating physicians, which have been found to have over 90% accuracy.[26] Thus, bias from misdiagnosis is likely to be modest.

A limitation that should be considered in interpreting the results of this study is that the exposure variables, including BMI, weight change, waist circumference, body area where weight is gained, and diabetes diagnosis, are based on self-report and thus may be subject to misclassification. In separate cohort studies, the validity of self-reported weight (r=0.98 in both NHS and HPFS),[27] waist circumference (0.98 in the HPFS and 0.91 in the NHS)[27] and self-reported diabetes (98% in the HPFS[28] and 97% in the NHS[29] of diabetes cases confirmed by medical record review), has been high. On the other hand, the validity of the self-reported location of weight gain is uncertain, and misclassification in this variable may have attenuated an existing relation with risk of PD.

The results of our study are overall consistent with those of a previous large longitudinal investigation among participants in the NHS and HPFS, in which neither obesity (at baseline or in young adulthood), abdominal obesity, or diabetes were significantly related to PD risk.[13, 19] The only noteworthy difference is that, in the NHS and HPFS, the authors reported that waist circumference and waist to hip ratio were associated with an increased risk of PD among never smokers,[13] whereas no relation between waist circumference (waist to hip ratio was not measured) and PD risk was found in this cohort.

In contrast to the mainland US, strong positive associations with PD were reported in a Finnish population for both obesity[11] and for diabetes.[18] The reasons for the difference between our results and those in the Finnish cohort are unclear. An important difference is that, in the Finnish study, the PD cases were identified through a link with a drug registry, and therefore only included PD cases who were taking anti-parkinsonian medications. Further, the Finnish study started in 1982, ten years earlier than our cohort, and the age at onset of PD in the Finnish cohort was 71.9 years in men and 71.2 years in women, approximately 9 and 6 years later than in our study. How such methodological and demographic differences could explain the conflicting results is, however, uncertain. Alternatively, a genetic factor predisposing to both obesity and PD may be present in the Finnish population and not in the mainland US. The main results of a study of 7,990 men of Asian descent in the Honolulu Heart Program (HHP) were intermediate between those from mainland US and those from Finland, in that no significant association was found with BMI,

but a positive association was found with other measures of fat distribution.[12] Because fat distribution is largely genetically determined [30], the latter finding is consistent with the notion that genetic factors may modify the relation between obesity and PD risk. Because diet, particularly fat composition, may explain this difference in results seen in Finnish and American cohorts, we examined in our cohort interactions between percent calories from saturated fat with obesity and diabetes. We did not observe any significant interactions in this analysis. To account for possible role of ancestry on the discrepancy between our results and those reported in the Finnish study, we also considered place of birth of the participant (categories: US; UK/Europe; Asia/Middle East; South America/Puerto Rico/Mexico) and place of birth of mother and father. We did not observe an interaction with any of these covariates and adding them to our models did not significantly alter the results.

In summary, in this large prospective study comprising mostly white Caucasian Americans, we found no relation between obesity, measures of central obesity, and diabetes with risk of developing Parkinson disease. These results confirm previous findings in a similar US population, but are discordant with results obtained in a Finnish cohort. This heterogeneity of results across populations with different ancestry raises the possibility of a genetic influence.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Study Funding: NIH R01 NS048517 to A. Ascherio and the Training Program in Environmental Epidemiology, NIH Kirshstein National Research Service Award, T32 ES07069 to N. Palacios

Natalia Palacios is supported by the Training Program in Environmental Epidemiology, NIH Kirshstein National Research Service Award, T32 ES07069.

Dr. Alberto Ascherio receives research funding from the National Institutes of Health, the Department of Defense, the Michael J. Fox Foundation, and the National Multiple Sclerosis Society. He received prior funding from Autism Speaks and honoraria for two scientific presentations to Merck Serono.

REFERENCES

1. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, Obesity, and Mortality from Cancer in a Prospectively Studied Cohort of U.S. Adults. N Engl J Med. 2003; 348(17):1625–1638. [PubMed: 12711737]
2. Petrelli JM, Calle EE, Rodriguez C, Thun MJ. Body mass index, height, and postmenopausal breast cancer mortality in a prospective cohort of US women. Cancer Causes Control. 2002; 13(4):325–332. [PubMed: 12074502]
3. Rimm EB, Stampfer MJ, Giovannucci E, et al. Body size and fat distribution as predictors of coronary heart disease among middle-aged and older US men. Am J Epidemiol. 1995; 141(12): 1117–1127. [PubMed: 7771450]
4. Manson JE, Colditz GA, Stampfer MJ, et al. A prospective study of obesity and risk of coronary heart disease in women. N Engl J Med. 1990; 322(13):882–889. [PubMed: 2314422]
5. Kahn SE, Hull RL, Utzschneider KM. Mechanisms linking obesity to insulin resistance and type 2 diabetes. Nature. 2006; 444(7121):840–846. [PubMed: 17167471]
6. Gustafson D, Rothenberg E, Blennow K, Steen B, Skoog I. An 18-Year Follow-up of Overweight and Risk of Alzheimer Disease. Arch Intern Med. 2003; 163(13):1524–1528. [PubMed: 12860573]
7. Michael MM, Serguei OF, Madhu V, et al. Hypothalamic dopamine and serotonin in the regulation of food intake. Nutrition (Burbank, Los Angeles County, Calif). 2000; 16(10):843–857.

8. Schwartz MW, Woods SC, Porte D, Seeley RJ, Baskin DG. Central nervous system control of food intake. Nature. 2000; 404(6778):661–671. [PubMed: 10766253]
9. William J, Langston LSF. The hypothalamus in parkinson disease. Annals of Neurology. 1978; 3(2): 129–133. [PubMed: 350130]
10. Shannak K, Rajput A, Rozdilsky B, Kish S, Gilbert J, Hornykiewicz O. Noradrenaline, dopamine and serotonin levels and metabolism in the human hypothalamus: observations in Parkinson's disease and normal subjects. Brain Research. 1994; 639(1):33–41. [PubMed: 8180836]
11. Hu G, Jousilahti P, Nissinen A, Antikainen R, Kivipelto M, Tuomilehto J. Body mass index and the risk of Parkinson disease. Neurology. 2006; 67(11):1955–1959. [PubMed: 17159100]
12. Abbott RD, Ross GW, White LR, et al. Midlife adiposity and the future risk of Parkinson's disease. Neurology. 2002; 59(7):1051–1057. [PubMed: 12370461]
13. Chen H, Zhang SM, Schwarzschild MA, Hernan MA, Willett WC, Ascherio A. Obesity and the risk of Parkinson's disease. Am J Epidemiol. 2004; 159(6):547–555. [PubMed: 15003958]
14. Logroscino G, Sesso H, Paffenbarger R Jr, Lee IM. Physical activity and risk of Parkinson's disease: a prospective cohort study. J Neurol Neurosurg Psychiatry. 2006; 77(12):1318–1322. [PubMed: 16926235]
15. Mokdad AH, Bowman BA, Ford ES, Vinicor F, Marks JS, Koplan JP. The continuing epidemics of obesity and diabetes in the United States. JAMA. 2001; 286(10):1195–1200. [PubMed: 11559264]
16. Mokdad AH, Ford ES, Bowman BA, et al. Prevalence of obesity, diabetes, and obesity-related health risk factors, 2001. JAMA. 2003; 289(1):76–79. [PubMed: 12503980]
17. Craft S, Stennis Watson G. Insulin and neurodegenerative disease: shared and specific mechanisms. The Lancet Neurology. 2004; 3(3):169–178.
18. Hu G, Jousilahti P, Bidel S, Antikainen R, Tuomilehto J. Type 2 diabetes and the risk of Parkinson's disease. Diabetes Care. 2007; 30(4):842–847. [PubMed: 17251276]
19. Simon KC, Chen H, Schwarzschild MA, Ascherio A. Hypertension, hypercholesterolemia, diabetes, and risk of Parkinson disease. Neurology. 2007; 69(17):1688–1695. [PubMed: 17761552]
20. Driver JA, Smith A, Buring JE, Gaziano JM, Kurth T, Logroscino G. Prospective Cohort Study of Type 2 Diabetes and the Risk of Parkinson's Disease. Diabetes Care. 2008; 31(10):2003–2005. [PubMed: 18599528]
21. Calle EE, Rodriguez C, Jacobs EJ, et al. The American Cancer Society Cancer Prevention Study II Nutrition Cohort: rationale, study design, and baseline characteristics. Cancer. 2002; 94(9):2490–2501. [PubMed: 12015775]
22. Chen H, Jacobs E, Schwarzschild MA, et al. Nonsteroidal antiinflammatory drug use and the risk for Parkinson's disease. Ann Neurol. 2005; 58(6):963–967. [PubMed: 16240369]
23. Patel AV, Rodriguez C, Bernstein L, Chao A, Thun MJ, Calle EE. Obesity, Recreational Physical Activity, and Risk of Pancreatic Cancer In a Large U.S. Cohort. Cancer Epidemiol Biomarkers Prev. 2005; 14(2):459–466. [PubMed: 15734973]
24. Ascherio A, Chen H, Weisskopf MG, et al. Pesticide exposure and risk for Parkinson's disease. Ann Neurol. 2006; 60:197–203. [PubMed: 16802290]
25. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986; 7(3):177–188. [PubMed: 3802833]
26. Hughes AJ, Daniel SE, Lees AJ. Improved accuracy of clinical diagnosis of Lewy body Parkinson's disease. Neurology. 2001; 57(8):1497–1499. [PubMed: 11673599]
27. Rimm EB, Stampfer MJ, Colditz GA, Chute CG, Litin LB, Willett WC. Validity of self-reported waist and hip circumferences in men and women. Epidemiology. 1990; 1(6):466–473. [PubMed: 2090285]
28. Hu FB, Leitzmann MF, Stampfer MJ, Colditz GA, Willett WC, Rimm EB. Physical Activity and Television Watching in Relation to Risk for Type 2 Diabetes Mellitus in Men. Arch Intern Med. 2001; 161(12):1542–1548. [PubMed: 11427103]
29. Manson JE, Stampfer MJ, Colditz GA, et al. Physical activity and incidence of non-insulin-dependent diabetes mellitus in women. The Lancet. 1991; 338(8770):774–778.

30. Heid IM, Jackson AU, Randall JC, et al. Meta-analysis identifies 13 new loci associated with waist-hip ratio and reveals sexual dimorphism in the genetic basis of fat distribution. Nat Genet. 42(11):949–960. [PubMed: 20935629]

Table 1

Relative risk of Parkinson's disease according to baseline body mass index (1992) and early adult body mass index (at age 18) and weight change since early adulthood, CPS-II Nutrition Cohort.

				Category of variable distribution		*p-trend* [§]	*p-heterogeneity* [^]
Variable	**1**	**2**	**3**	**4**	**5**		
Body Mass Index [*] in 1992 [#]	**18.5 -23**	**23-24.9**	**25-26.9**	**27-29.9**	**>=30**		
Men							
No. cases	62	88	122	95	46		
No. PY	104352	167751	201441	185469	106924		
RR[1]	1.0 (Ref)	0.91 (0.66, 1.27)	1.11 (0.82, 1.52)	0.98 (0.71, 1.36)	0.86 (0.58, 1.27)		
RR[2]	1.0 (Ref)	0.93 (0.67, 1.28)	1.17 (0.86, 1.59)	1.06 (0.77, 1.47)	0.98 (0.66, 1.46)	0.80	
Women							
No. cases	72	52	28	41	33		
No. PY	300682	199658	156020	150220	148417		
RR[1]	1.0 (Ref)	1.06 (0.74, 1.52)	0.71 (0.46, 1.11)	1.10 (0.75, 1.61)	0.96 (0.63, 1.45)		
RR[2]	1.0 (Ref)	1.08 (0.76, 1.55)	0.73 (0.47, 1.14)	1.18 (0.80, 1.74)	1.02 (0.66, 1.56)	0.91	
Men and Women							
RR[2]		1.00 (0.78, 1.26)	0.95 (0.60, 1.50)	1.11 (0.86, 1.42)	1.00 (0.75, 1.34)	0.79	0.94
Body Mass Index at age 18	**<20**	**20-22.4**	**22.5-24.9**	**25-26.9**	**>=27**		
Men							
No. cases	106	160	90	37	18		
No. PY	203070	276690	174326	67257	38329		
RR[1]	1.0 (Ref)	1.13 (0.88, 1.45)	1.05 (0.79, 1.39)	1.16 (0.79, 1.69)	1.04 (0.63, 1.72)		
RR[2]	1.0 (Ref)	1.12 (0.87, 1.43)	1.05 (0.79, 1.39)	1.19 (0.82, 1.74)	1.06 (0.64, 1.74)	0.61	
Women							
No. cases	99	82	34	9	8		
No. PY	429135	359543	120963	29410	28460		
RR[1]	1.0 (Ref)	1.01 (0.75, 1.36)	1.24 (0.83, 1.83)	1.43 (0.72, 2.85)	1.35 (0.65, 2.80)		

			Category of variable distribution			*p-trend* [§]	*p-heterogeneity* [^]
Variable	**1**	**2**	**3**	**4**	**5**		
RR[2]	1.0 (Ref)	1.02 (0.76, 1.37)	1.23 (0.83, 1.83)	1.43 (0.71, 2.84)	1.36 (0.66, 2.82)	0.17	
Men and Women							
RR[2]		1.08 (0.89, 1.30)	1.11 (0.88, 1.40)	1.24 (0.89, 1.73)	1.15 (0.76, 1.73)	0.23	0.40
Weight change between age 18 and 1992[#] (pounds[**])	**5lb loss to 5lb gain**	**5-14.9lb gain**	**15-24.9lb gain**	**25-44.9lb gain**	**>=45lb gain**		
Men							
No. cases	30	49	76	137	105		
No. PY	30920	96759	132361	252474	217365		
RR[1]	1.0 (Ref)	0.51 (0.32, 0.81)	0.59 (0.38, 0.89)	0.57 (0.38, 0.84)	0.53 (0.35, 0.80)		
RR[2]	1.0 (Ref)	0.51 (0.32, 0.80)	0.58 (0.37, 0.89)	0.56 (0.37, 0.84)	0.54 (0.35, 0.85)	0.36	
Women							
No. cases	20	41	43	58	52		
No. PY	66150	151042	174495	285362	229905		
RR[1]	1.0 (Ref)	0.92 (0.54, 1.58)	0.83 (0.49, 1.41)	0.68 (0.41, 1.13)	0.74 (0.44, 1.25)		
RR[2]	1.0 (Ref)	0.93 (0.54, 1.60)	0.80 (0.46, 1.40)	0.63 (0.35, 1.11)	0.62 (0.32, 1.21)	0.06	
Men and Women							
RR[2]		0.68 (0.38, 1.22)	0.65 (0.46, 0.90)	0.58 (0.42, 0.81)	0.56 (0.39, 0.82)	0.08	0.26

[*] Weight (kg)/height(m)^2

[#] study baseline

[**] 1 pound = 0.45 kg

[1] *adjusted for age in months and smoking in quintiles of pack years

[2] *adjusted for age in months and smoking in quintiles of pack years, alcohol intake, caffeine intake, calories, dairy intake, physical activity, pesticide exposure and education

[§] trend tests conducted in multivariate models

[^] p-heterogeneity comparing analyses including only men to those including only women

Table 2

Relative risk of Parkinson's disease according to waist circumference and self-reported location of weight gain.

Variable	Category of variable distribution					*p-trend* [§]	*p-heterogeneity*[^]
	1	**2**	**3**	**4**	**5**		
Waist Circumference in 1997 (inches[*])							
Men	**<34.5**	**34.5-36.2**	**36.3-37.9**	**38.0-40.2**	**>=40.3**		
No. cases	31	48	20	72	78		
No. PY	52356	74371	33559	118397	108195		
RR[1]	1.0 (Ref)	1.07 (0.68, 1.68)	0.98 (0.56, 1.71)	1.01 (0.66, 1.54)	1.22 (0.81, 1.86)		
RR[2]	1.0 (Ref)	1.07 (0.68, 1.69)	1.01 (0.57, 1.77)	1.10 (0.72, 1.69)	1.39 (0.91, 2.12)	0.08	
Women	<28.0	28.0-29.9	30.0-31.9	32.0-34.9	>=35.0		
No. cases	11	20	22	27	62		
No. PY	41494	61427	72360	111956	187545		
RR[1]	1.0 (Ref)	1.21 (0.58, 2.51)	1.10 (0.53, 2.28)	0.85 (0.42, 1.73)	1.19 (0.62, 2.26)		
RR[2]	1.0 (Ref)	1.16 (0.55, 2.43)	1.06 (0.51, 2.20)	0.87 (0.43, 1.76)	1.26 (0.65, 2.41)	0.39	
Men and Women							
RR[2]		1.09 (0.74, 1.61)	1.03 (0.66, 1.61)	1.03 (0.72, 1.49)	1.35 (0.95, 1.93)	0.08	0.65
Self-reported location of weight gain		**Peripheral weight gain** [£]		**Central weight gain** [£]			
Men							
No. cases		154		266			
No. PY		267571		511106			
RR[1]		1.0 (Ref)		0.93 (0.76, 1.14)			
RR[2]		1.0 (Ref)		0.91 (0.74, 1.11)		0.35	
Women							
No. cases		191		45			
No. PY		781855		203994			
RR[1]		1.0 (Ref)		0.85 (0.61, 1.17)			
RR[2]		1.0 (Ref)		0.85 (0.61, 1.19)		0.35	

Variable	Category of variable distribution					*p-trend* §	*p-heterogeneity*^
	1	2	3	4	5		
Men and Women							
RR[2]				0.89 (0.75, 1.06)		0.20	0.75

*1 inch = 2.54 cm

[1]*adjusted for age in months and smoking in quintiles of pack years

[2]*adjusted for age in months and smoking in quintiles of pack years, alcohol intake, caffeine intake, calories, dairy intake, pesticide exposure, physical activity, and education

§trend tests conducted in multivariate models

£central weight gain was defined as reported weight gain in the chest and shoulders or waist, and peripheral weight gain was defined as reported weight gain in hips and thighs or equally all over

^p-heterogeneity comparing analyses including only men to those including only women

Table 3

Relative risk of Parkinson's disease according to baseline diabetes mellitus diagnosis.

Diabetes Reported in 1992	No	Yes	*p-trend* §	*p-heterogeneity* ^
Men*				
No. cases	338	24		
No. PY	62367	52731		
RR[1]	1.0 (Ref)	0.82 (0.54, 1.24)		
RR[2]	1.0 (Ref)	0.87 (0.57, 1.33)	0.47	
Women*				
No. cases	191	11		
No. PY	797915	48194		
RR[1]	1.0 (Ref)	0.87 (0.47, 1.60)		
RR[2]	1.0 (Ref)	0.90 (0.48, 1.66)	0.67	
Men and Women				
RR[2]		0.88 (0.62, 1.25)	0.40	0.96

[1] *adjusted for age in months and smoking in quintiles of pack years

[2] *adjusted for age in months and smoking in quintiles of pack years, alcohol intake, caffeine intake, calories, dairy intake, pesticide exposure, physical activity and education

§ trend tests conducted in multivariate models

^ p-heterogeneity comparing analyses including only men to those including only women