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General and abdominal adiposity and the risk of Parkinson's disease: A prospective cohort study

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ABSTRACT

Introduction: Due to demographic change, an increase in the frequency of Parkinson's disease (PD) patients is expected in the future and, thus, the identification of modifiable risk factors is urgently needed. We aimed to examine the associations of body mass index (BMI) and waist circumference (WC) with incident PD.

Methods: In 13 of the 23 centers of the European Prospective Investigation into Cancer and Nutrition (EPIC) study, a total of 734 incident cases of PD were identified between 1992 and 2012 with a mean follow-up of 12 years. Cox proportional hazards regression was used to calculate hazard ratios (HR) with 95% confidence intervals (CI). We modelled anthropometric variables as continuous and categorical exposures and performed subgroup analyses by potential effect modifiers including sex and smoking.

Results: We found no association between BMI, WC and incident PD, neither among men nor among women. Among never and former smokers, BMI and waist circumference were also not associated with PD risk. For male smokers, however, we observed a statistically significant inverse association between BMI and PD risk (HR 0.51, 95%CI: 0.30, 0.84) and the opposite for women, i.e. a significant direct association of BMI (HR 1.79, 95%CI: 1.04, 3.08) and waist circumference (HR 1.64, 95%CI: 1.03, 2.61) with risk of PD.

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Conclusion: Our data revealed no association between excess weight and PD risk but a possible interaction between anthropometry, sex and smoking.

1. Introduction

Parkinson's disease (PD) is the second most common late onset neurodegenerative disease, following Alzheimer's Disease, with an incidence between 10 and 18 cases per 100,000 person-years [1–3]. Incidence rates are highest in (and post) the 7th decade with age being the greatest risk factor for PD, while pathological changes preceding clinical symptomatology typically occur already at the age of 50 [4]. The disease is generally more common among men than among women [4]. Due to a rising life expectancy worldwide, the number of people with PD are expected to appreciably increase in the near future [5]. Hence, development of effective disease modifying therapies and identification of modifiable risk factors that would allow primary prevention of PD are urgently needed [1,2,4]. While the precise biological mechanisms underpinning the etiology of PD still remain unknown, the disease is thought to result from complex interactions between genetic and environmental factors. A limited number of risk factors beyond age and sex have already been discovered. Those include rural living, agricultural occupation, pesticide exposure, well-water drinking, beta-blocker use, and prior head injury [1]. Alcohol consumption, calcium channel blocker use, coffee consumption and non-steroidal anti-inflammatory drug use have been associated with relative risk reductions [1], and interestingly and most controversial, numerous epidemiologic studies showed that tobacco smoking could also be a protective factor for PD [6–8]. The role of excess body weight and its association with PD risk is still unclear [1,9,10].

The pathological hallmark of PD is a loss of dopaminergic neurons in the substantia nigra pars compacta [1]. Of note, a decrement of dopamine - D_2 – receptor availability has been reported in obese PD patients, in proportion to their body-mass-index (BMI) [11]. Obesity is known to be pro-inflammatory; thus, obesity induced chronic inflammation may lead to higher vulnerability to neurotoxins and/or increased neurotoxin levels and a decrease of dopamine receptor availability, which may increase the risk of developing PD [12]. By contrast, a low BMI has been associated with a decline in cognitive function in the elderly and has also been suggested as a predictor for PD [13]. So far, excess BMI has been investigated as a risk factor in several prospective cohort studies and summarized in two overlapping meta-analyses [9,10]. The latest meta-analysis based on 10 cohort studies did not find any consistent association between obesity and PD [9]. Waist circumference, a surrogate for visceral body fat, was not associated with risk of PD in two prospective investigations [14,15].

These inconsistencies regarding the possible relationship between anthropometric indices of adiposity and PD risk prompted us to examine the associations of two main anthropometric indices with the future risk of PD, by sex and by smoking status, in a large European multi-center population-based cohort.

2. Methods

2.1. Study population

The current study is part of the population-based European Prospective Investigation into Cancer and Nutrition (EPIC) study [16,17]. The EPIC cohort consists of 519,978 participants (366,521 men and 153,457 women), recruited between 1992 and 2000 in 23 centers across 10 European countries, mainly drawn at random from the general population with the exception of Utrecht, where participants were part of a breast cancer screening program, and Spain and Italy, where participants were recruited from the general population as well as from selected enterprises and blood banks [17]. Thirteen of the 23 centers collected information on neurodegenerative disorders at baseline during follow-up and formed the so called NeuroEPIC4PD study, with the aim to investigate risk factors of neurodegenerative disorders. The NeuroEPIC4PD study included 220,494 participants from the following 13 centers in 7 of the 10 European countries: Sweden (Umeå, Malmo), the Netherlands (Utrecht), United Kingdom (Cambridge), Germany (Heidelberg), Spain (San Sebastian, Navarra, Murcia), Italy (Turin, Varese, Florence, Naples), and Greece (country-wide). The EPIC centers in Denmark, Norway and France were not included in the current study due to unavailability of data on neurodegenerative disorders. A total of 137,174 of the NeuroEPIC4PD cohort were women (62.2%) and 83,320 were men (37.8%) [16]. This study was approved by local Ethical Committees. All participants signed a consent form for the use of the obtained data.

2.2. Case ascertainment and sample size

To maximize sensitivity, potential PD cases were identified by each center via record linkage with hospital records, hospital discharge files, outpatient/primary health care records, drug prescription registries and/or mortality records (Umeå, Malmo, San Sebastian, Navarra, Murcia), through active follow-up via self-reported questionnaires and/or interviews (Utrecht, Greece) or both (Cambridge, Heidelberg, Turin, Varese, Florence, Naples) [16]. In this process 1723 potential cases of PD and Parkinson related diseases where identified and their clinical records were reviewed by neurologists specialized in movement disorders [16]. Each case was either labeled as “definite“, “very likely“, “probable“ or “possible“, based on their likelihood of diagnosis which depended on the quality of data and the confidence of the diagnosing neurologist (e.g. “definite” if the confidence of the neurologist was high and the quality of data was excellent) [16]. Cases that failed to be labeled even as possible were not qualified and were excluded from the analysis [16]. This led to overall 881 identified cases of PD, 230 participants with parkinsonian-related disorders (e.g. multiple system atrophy) and 225 with unrelated conditions, while 387 potential cases were excluded because of missing clinical data [16]. We subsequently excluded 147 prevalent PD cases at baseline, leaving a total sample of 734 incident PD cases diagnosed between 1992 and 2012, with a mean follow-up time of 12 years (range: 0–21) and, thus, a total of 220,347 participants. For a more detailed description of case ascertainment methods we refer to Gallo et al., 2015 [16].

2.3. Lifestyle characteristics

Data on lifestyle and diet were collected through self-administered questionnaires or interviews at baseline [17]. Information on smoking status was available for 715 out of 734 incident cases of PD. Smoking was either defined as current, when the participant was smoking any number of smoking devices per day (cigars, cigarettes, pipes) at baseline, former, when the participant was ever smoking in the past, and never, when the participant has never smoked in his or her lifetime. Information on lifetime number of cigarettes/day was only obtained in 73,787 participants (including 181 PD cases) and on duration of smoking only in 107,752 participants (including 284 PD cases). Body weight and height, as well as waist and hip circumference were measured at enrolment by trained observers, using a standardized protocol in the majority of centers [17,18]. In the Umeå sub-cohort, no data on waist and hip circumference were obtained [18]; thus, our analyses on waist circumference were limited to 679 out of 734 cases. Details on

anthropometric measurements in EPIC were described elsewhere [18]. Body-Mass-Index (BMI) was used as an indicator for general obesity and was calculated by dividing weight (in kilograms) by the square of height (in meters). Waist circumference was analyzed as an indicator for central/abdominal obesity.

2.4. Statistical analysis

Cox proportional hazards regression was used to calculate hazard ratios (HR) with 95% confidence intervals (CI) with age as the time variable, PD as the outcome and adiposity indices as the exposure variables. To account for death as a competing risk, we right-censored our data at end of follow-up or death, whichever occurred first. All analyses were performed for men and women separately to account for different PD prevalence by sex [4]. In the basic model, we adjusted for age at recruitment and center. We conducted a multivariable adjusted model adjusted for age at recruitment, center, highest school level as a proxy for socio-economic status, physical activity according to the Cambridge Physical Activity Index [19] (inactive, moderately inactive, moderately active, active), coffee intake (ml/day), alcohol consumption at recruitment (g/day) and in smokers additionally for age at starting smoking, number of average lifetime cigarettes per day, lifetime duration of smoking, smoking status at recruitment and time since quitting smoking (if never smoker). These potential confounders have been discussed as possible risk factors of PD [1,9,20]. We tested the validity of the proportional hazard assumption with Schoenfeld residuals. We performed a continuous analysis where the HR referred to a change in BMI by 5 units and in waist circumference by 10 units. In addition, we also performed categorical analyses using pre-defined cut-points for BMI ($< 25\,kg/m^2$, $25–30\,kg/m^2$, $\geq 30\,kg/m^2$ and $= < 26\,kg/m^2$ vs. $> 26\,kg/m^2$ (median)) and waist circumference (men: < 94 cm, 94–102 cm, ≥102 cm; women: < 80 cm, 80–88 cm, ≥88 cm). We did not specifically investigate underweight (BMI $< 18.5\,kg/m^2$) due to a limited number of PD cases (n = 7) in that group. All analyses on waist circumference were adjusted for height. Validity of the linearity assumption was tested by using restricted cubic spline regression which did not show strong evidence of deviation from linearity in our main model. Further, we conducted subgroup analyses by smoking status (never, former, current). Heterogeneity by these suspected effect modifiers was assessed with Wald-statistics. In addition, we conducted a Cox regression analysis of smoking status and PD risk stratified by median BMI and median waist circumference to explore the complexity in the triangle overweight – smoking – PD. We repeated the main analyses by restricting the dataset to the "definite" and "very likely" diagnoses. To investigate possible reverse causation, we excluded diagnosed cases within the first 5 and 10 years after baseline and included cases diagnosed within 1 year prior to baseline. We did not adjust our significance value of $p < 0.05$ for multiple testing because we only assessed two exposures and one outcome with a total number of 16 performed analyses (excluding sensitivity analysis). All statistical analyses were conducted using SAS, version 9.4 (SAS Institute, Cary, NC).

3. Results

Main characteristics of our cohort are shown in Table 1. Although the NeuroEPIC4PD-cohort included considerably more women (62%) than men (38%), numbers of PD cases in the cohort were approximately equal between men (n = 378; 51%) and women (n = 356; 49%), confirming the higher incidence of PD among men (cumulative incidence: 0.45% vs. 0.26%). Mean age of study participants at baseline was 62 years (range 30–77) for cases and 53 years (range 19–86) for participants who did not develop PD, i.e. non-cases. Mean age of onset of PD

Table 1
Baseline characteristics of the NeuroEPIC4PD cohort, 1992–2012.

	Men (n = 83,240)		Women (n = 137,107)		All (n = 220,347)	
	PD (n = 378)	Non-PD (n = 82,862)	PD (n = 356)	Non-PD (n = 136,751)	PD (n = 734)	Non-PD (n = 219,613)
Age at Recruitment, mean (min, max)	62 (30, 77)	53 (19, 86)	61 (30, 76)	53 (20, 84)	62 (30, 77)	53 (19, 86)
Age at PD onset, mean (min, max)	70 (41, 86)	–	69 (37, 87)	–	69 (37, 87)	–
BMI, mean (SD)	27 (4)	27 (4)	27 (4)	26 (5)	27 (4)	26 (4)
Waist circumference, mean (SD)*	97 (10)	95 (10)	84 (11)	82 (12)	90 (13)	87 (13)
Body height, mean (SD)	173 (8)	174 (7)	159 (7)	161 (7)	166 (10)	166 (9)
Level of Education, n (%)						
Primary school	205 (56)	35,024 (43)	205 (59)	62,737 (47)	410 (57)	97,761 (45)
Secondary/professional school	111 (30)	30,425 (37)	106 (30)	50,046 (37)	217 (30)	80,471 (37)
Longer education (University)	52 (14)	15,785 (19)	37 (11)	22,106 (16)	89 (12)	37,891 (18)
Physical activity Index, n (%)						
Inactive + moderately inactive	212 (63)	43,498 (63)	107 (33)	40,070 (33)	319 (48)	83,568 (44)
Moderately active + active	126 (37)	25,375 (37)	214 (67)	81,614 (67)	340 (52)	106,989 (56)
Alcohol intake (g/day), mean (SD)**	16 (18)	19 (23)	5 (7)	7 (11)	10 (15)	11 (18)
Coffee intake (ml/day), mean (SD)***	274 (285)	322 (324)	277(293)	310 (306)	275 (288)	315 (313)
Age started smoking, mean (SD)****	19 (6)	19 (5)	26 (10)	21 (7)	21 (8)	20 (6)
Lifetime number of cigarettes/day, mean (SD)*****	15 (10)	17 (10)	8 (6)	11 (7)	13 (10)	14 (9)
Time since quitting smoking, mean (SD) ******	21 (13)	16 (11)	18 (12)	15 (10)	20 (13)	15 (10)
Duration of smoking (years), n (%)						
< 20	64 (32)	16,803 (33)	38 (45)	23,384 (41)	102 (36)	40,187 (37)
21-40	91 (46)	27,308 (54)	36 (42)	28,928 (51)	127 (45)	56,236 (52)
> 40	44 (22)	6743 (13)	11 (13)	4302 (8)	55 (19)	11,045 (10)
Smoking status, n (%)						
Never	149 (41)	27,041 (34)	253 (72)	75,140 (56)	402 (56)	102,181 (48)
Former	165 (45)	30,056 (37)	67 (19)	29,726 (22)	232 (32)	59,782 (28)
Current	52 (14)	23,123 (29)	29 (8)	29,165 (22)	81 (11)	52,288 (24)
Menopausal status, n (%)						
Premenopausal			30 (9)	40,317 (37)		
Postmenopausal			290 (91)	69,269 (63)		
Hormone replacement therapy, n (%)						
Use at baseline			40 (12)	15,322 (12)		
No use at baseline			288 (88)	112,925 (88)		

*n = 194,631 including 679 PD cases; **n = 214,117 including 695 PD cases; ***n = 214,115 including 695 PD cases; ****n = 109,476 including 296 PD cases; *****n = 73,787 including 181 PD cases; ******n = 57,790 including 217 PD cases. n = number of study participants.

Table 2
Associations between anthropometric indices and risk of PD, overall and by smoking status, 1992–2012.

	Men [HR (95%CI)]				Women [HR (95%CI)]			
	All men[X]	Never Smoker	Former Smokers	Current Smoker	All women[X]	Never Smoker	Former Smokers	Current Smoker
BMI, per 5 kg/m^2	PD cases = 378	PD cases = 149	PD cases = 165	PD cases = 52	PD cases = 356	PD cases = 253	PD cases = 67	PD cases = 29
Crude*	0.86 (0.74,1.01)	0.98 (0.75,1.26)	0.84 (0.66,1.07)	0.53 (0.32,0.88)	1.03 (0.90,1.17)	1.02 (0.87,1.20)	0.87 (0.63,1.20)	1.63 (1.08,2.46)
Adjusted #	0.86 (0.73,1.01)	0.97 (0.75,1.26)	0.84 (0.66,1.08)	0.51 (0.30,0.84)	1.01 (0.88,1.15)	1.02 (0.86,1.20)	0.86 (0.62,1.19)	1.79 (1.04,3.08)
			P-het < 0.001$				P-het = 0.093$	
BMI, sensitivity analysis~	PD cases = 197	PD cases = 81	PD cases = 86	PD cases = 25	PD cases = 200	PD cases = 147	PD cases = 35	PD cases = 15
Crude*	1.03 (0.83,1.28)	1.16 (0.81,1.66)	0.91 (0.65,1.27)	0.65 (0.30,1.38)	1.11 (0.92,1.33)	1.20 (0.97,1.49)	0.51 (0.29,0.92)	2.01 (0.86,4.72)
Adjusted #	1.02 (0.82,1.28)	1.11 (0.75,1.62)	0.95 (0.68,1.33)	0.58 (0.26,1.33)	1.08 (0.89,1.31)	1.19 (0.96,1.49)	0.57 (0.31,1.03)	1.66 (0.35,7.97)
BMI, excl.5 years	PD cases = 267	PD cases = 109	PD cases = 111	PD cases = 39	PD cases = 244	PD cases = 175	PD cases = 42	PD cases = 23
Crude*	0.82 (0.67,1.00)	1.02 (0.75,1.40)	0.74 (0.54,1.01)	0.56 (0.30,1.03)	1.02 (0.87,1.21)	1.05 (0.86,1.28)	0.75 (0.48,1.16)	1.69 (0.98,2.93)
Adjusted #	0.83 (0.68,1.01)	1.00 (0.72,1.39)	0.75 (0.54,1.03)	0.49 (0.25,0.96)	1.00 (0.84,1.18)	1.05 (0.85,1.29)	0.69 (0.44,1.09)	2.38 (1.07,5.29)
			P-het = 0.002$				P-het = 0.163$	
Waist, per 10 cm	PD cases = 349	PD cases = 129	PD cases = 158	PD cases = 50	PD cases = 330	PD cases = 234	PD cases = 62	PD cases = 27
Crude*	1.02 (0.91,1.14)	1.17 (0.96,1.42)	0.95 (0.80,1.13)	0.79 (0.56,1.10)	0.99(0.89,1.11)	0.98 (0.86,1.12)	0.92 (0.71,1.19)	1.52 (1.08,2.15)
Adjusted # +	1.01 (0.89,1.13)	1.14 (0.93,1.40)	0.95 (0.80,1.13)	0.75 (0.52,1.06)	0.98 (0.88,1.10)	0.97 (0.85,1.12)	0.92 (0.71,1.19)	1.64 (1.03,2.61)
			P-het = 0.002$				P-het = 0.104$	
Waist, sensitivity analysis~	PD cases = 173	PD cases = 65	PD cases = 79	PD cases = 24	PD cases = 177	PD cases = 131	PD cases = 30	PD cases = 13
Crude*	1.08 (0.92,1.27)	1.22 (0.91,1.64)	0.97 (0.77,1.24)	0.92 (0.55,1.56)	0.97 (0.83,1.14)	1.02 (0.84,1.23)	0.66 (0.41,1.07)	1.63 (0.74,3.58)
Adjusted #	1.05 (0.89,1.25)	1.13 (0.82,1.55)	0.97 (0.76,1.24)	0.86 (0.48,1.52)	0.98 (0.83,1.16)	1.02 (0.84,1.23)	0.76 (0.46,1.25)	1.35 (0.18,10.37)
Waist, excl.5 years	PD cases = 240	PD cases = 91	PD cases = 104	PD cases = 37	PD cases = 223	PD cases = 158	PD cases = 40	PD cases = 21
Crude*	0.94 (0.81,1.08)	1.14 (0.89,1.46)	0.83 (0.66,1.03)	0.83 (0.55,1.27)	0.99 (0.86,1.14)	0.98(0.83,1.16)	0.86 (0.61,1.20)	1.63 (0.98,2.71)
Adjusted # +	0.93 (0.80,1.08)	1.08 (0.83,1.40)	0.83 (0.66,1.05)	0.85 (0.54,1.35)	0.97 (0.84,1.12)	0.97 (0.82,1.16)	0.83 (0.58,1.17)	2.15 (1.04,4.44)
			P-het = 0.005$				P-het = 0.238$	

*Adjusted for age at recruitment, center.
#Adjusted for age at recruitment, center, school level, physical activity, coffee intake, alcohol consumption, age at starting smoking, number of average lifetime cigarettes per day, lifetime duration of smoking, smoking status at recruitment, time since quitting smoking and sex (if men and women combined).
+Adjusted additionally for height.
~Sensitivity Analysis: restricted dataset, including only cases with "definite" and "very likely" probability of diagnosis.
$Heterogeneity between current smokers, formers smokers and never smokers (women and men separately)Heterogeneity between current smokers and never smokers (BMI): men p-het < 0.001; women p-het = 0.05.
[X] "All" includes all current smokers, all former smokers, all never smokers plus all subjects with missing information about smoking (men: n = 12, women: n = 7) n = number of study participants.

motor symptomatology was 70 (range 41–86) years in men and 69 (range 37–87) in women. Participants who were diagnosed with PD during follow-up consumed less alcohol and coffee at baseline than the comparison group of non-PD cases, irrespective of their sex. Smoking at baseline was less common among men and women with later PD (14% and 8%, respectively) than among the non-cases (29% and 22%, respectively).

3.1. Associations of overweight with risk of PD

Among men and women, neither BMI (per 5 kg/m^2, HR 0.86, 95%CI: 0.73, 1.01 and HR 1.01, 95%CI 0.88, 1.15, respectively) nor waist circumference (per 10 cm, HR 1.01, 95%CI 0.89, 1.13 and HR 0.98, 95%CI 0.88, 1.10, respectively) were significantly associated with PD risk. Using categorical instead of continuous variables resulted in comparable risk associations (Supplementary Tables 1 and 2).

3.2. Effect modification by smoking status

We observed heterogeneity by smoking status (never vs. current) in the association between BMI and PD risk (men: p-het < 0.001, women: p-het = 0.05) (Table 2). Among never and former smokers, neither BMI nor waist circumference were significantly associated with PD risk. Among current smokers at baseline, BMI was inversely associated with risk of PD among men (HR 0.51, 95%CI: 0.30, 0.84), in contrast to a direct association in women (HR 1.79, 95%CI: 1.04, 3.08, p-het < 0.001 between men and women among current smokers). Associations in similar magnitude were also observed for waist circumference among smoking women (HR 1.64, 95%CI: 1.03, 2.61) but not men.

3.3. Exploratory analyses smoking – BMI

To further elucidate these complex interactions, we alternatively examined the associations of smoking status with PD risk by strata of BMI (Supplementary Table 3). In this analysis, current compared to never smoking was inversely associated with PD risk (HR 0.40, 95%CI: 0.24, 0.66) among men with a BMI above 26 kg/m^2, but not among men with BMI $\leq$26 kg/m^2 (median). In contrast, an inverse association of current smoking with PD risk was observed in leaner (BMI $\leq$26 $kg/m^{2;}$ (HR 0.36, 95%CI: 0.19, 0.66), but not in more obese women.

3.4. Sensitivity analyses

Exclusion of PD cases that were diagnosed within the first five or ten years (data for 10 years not shown) after baseline and inclusion of cases diagnosed within 1 years prior to baseline did either not or only marginally influence any association between anthropometric measures and risk of PD. The only exceptions are the associations of BMI and waist circumference with risk of PD among smoking women, where risk estimates became even stronger after the exclusion of those cases that were diagnosed within 5 years after baseline (Table 2). Restricting the analysis to cases with the aforementioned diagnosis probability labeled as “very likely” or “definite” (n = 397) did not result in significant associations of BMI or waist circumference with PD risk, irrespective of the participant's smoking status (Table 2).

4. Discussion

In this European cohort with more than 700 incident PD cases, we found no association between BMI, waist circumference and incident PD, neither among men nor among women. We found an association of BMI or waist circumference with PD risk that depended on individuals' smoking status and sex but that lost significance after the exclusion of less certain cases.

Among women and men, we found that BMI was not associated with risk of PD, which is in line with findings of the most recent and comprehensive meta-analysis of prospective cohort studies [9] and with the majority of published prospective cohort studies within. By contrast, two Finnish cohorts in the meta-analyses found a positive association between BMI and PD risk [21,22]: in one the association was irrespective of smoking history [21] and in the other the association was observed only after excluding PD cases diagnosed within the first 15 years of follow-up [22]. Because only a few cases in our study were diagnosed that late during follow-up (40 cases), we were unable to replicate the latter finding. In both studies, the prospective case ascertainment relied on a registry for drug costs for all PD-patients in Finland, who were diagnosed by a physician and whose diagnosis was confirmed by a neurologist of the Social Insurance Institution [21,22]. One of these studies also re-evaluated retrospectively the diagnoses by a study neurologist which led to the exclusion of 20% of the cases [22]. Using the drug registry for case ascertainment might have led to the exclusion of mild cases of PD, as already pointed out by Hu et al., 2006 [21].

Smoking status as an effect modifier was only investigated in one of these studies but without a differentiation between current and former smokers and with no evident interaction [21]. The more recent study did not account for a possible effect modification by smoking history although there was evidence of an unadjusted difference in mean BMI (BMI among never and past smokers: 27.2 kg/m^2, BMI among smokers: 25.0 kg/m^2) [22]. While cohorts of both studies were small (n = 45,806 and n = 6715) compared to our cohort (n = 220,494), they included a very high number of cases (n = 526 and n = 101), which is most likely the consequence of their longer average follow-up times (19 years and 22 years), as compared to 12 years in the present dataset. These study characteristics may explain the divergent findings between the Finnish cohorts and ours. A long follow-up may increase the likelihood of people changing their smoking habits and their weight prior of a possible PD diagnosis, resulting in biased risk estimates that rely on baseline assessments. However, these are mere speculations and the reasons for the divergent results remain unclear. A recently published Mendelian randomization study with 13,708 cases of PD found an inverse association of BMI with the risk of PD (OR 0.82, 95%CI: 0.69, 0.98) [23]. However, the analysis by strata of smoking status could not be performed on aggregated data and, thus, the possibility that their observed association may be largely driven by the strong interaction between smoking status, BMI and sex could not be assessed.

In our study, waist circumference was associated with a 1.6-fold higher PD risk in smoking women but not in men or non-smokers, suggesting that the location of body fat in combination with smoking status might have an influence on risk of PD depending on individuals' sex. By contrast, Chen et al., 2004 observed in two US cohorts no association between waist circumference and PD risk among ever smokers (i.e. smokers and former smokers) but a direct association in a comparable magnitude among never smoking men and women combined [14]. Palacios et al., 2011 conducted an analysis stratified by smoking status and found no association between waist circumference and PD risk, neither among never smokers nor among ever smokers in a further US cohort [15]. In contrast to our study where measurement of the majority of anthropometric indices was performed by trained observers, all three studies relied on self-reported and self-measured data on waist circumference [14,15]. The studies did not differentiate between former and current smokers [14,15], thus, a possible difference between those two groups could not be investigated.

Obesity has been controversially discussed in regards to its biological impact on PD: on the one hand possibly increasing the risk by decreasing the availably of dopamine receptors and increasing the vulnerably to neurotoxins [12], on the other hand leaner subjects tend to have a higher risk of cognitive decline [13] and PD patients gaining weight following deep brain stimulation [24]. The difference in prevalence between men and women let to the idea that estrogen might have an protective effect on PD [25]. Smoking has been described as a protective factor against PD [6] by weakening the effect of different

neurotoxins and improving the dopamine effect in both sexes [26] which is consistent with our data (overall HR for current smokers compared to never smokers 0.49, 95%CI: 0.38, 0.63 [27]). Paradoxically, we found that in men smoking was associated with reduced PD risk only for those who were overweight (BMI > 26 kg/m^2), whilst in women this association was observed only for those who were comparably leaner (BMI ≤26 kg/m^2), which clarifies, why we did not see any strong inverse association in the continuous model with an elevated BMI among smoking women. However, one has to bear in mind that number of overweight women who smoked and developed PD during follow-up was small with 17 in total. The possible interaction between smoking, BMI and sex may, indeed, result from a complex interplay of competing risks (primarily death such as in the subgroup of smoking men, where the inverse association between BMI and PD could be due to early deaths of overweight smoking men), hormones, as well as long-term effects of heavy smoking on body composition; for instance, it has been reported that sub-groups of long-term, heavy smokers are characterized by extreme leanness [28]. Also, time from cessation of smoking can impact time spent overweight, and therefore duration of adipose related inflammation. There are no obvious plausible biological explanations for the divergent results and they are subject to speculation. Is adiposity influencing the complex protective effect of smoking on PD risk depending on sex and, hence, individuals' hormone status? Our sensitivity analysis and the lack of association between waist circumference and PD risk among male smokers show that they need to be interpreted with caution. Further investigations in well-powered studies including biomarker assessments are necessary to not only verify our results but also to unravel the biological nature of the associations.

Whatever the explanation, the associations of BMI or waist circumference with PD risk among current smokers may primarily reflect an effect of smoking, whereas the lack of association of PD risk with either BMI or waist circumference among never smokers suggests an absence of a main effect of chronic, adiposity-related inflammation with PD development.

A major strength of our investigation is the largest number of PD-cases among all cohort studies on PD and its anthropometric risk factors. The diagnosis of PD was ensured through three phases of case ascertainment, increasing validity [16]. In that process 387 possible cases were excluded because of lacking clinical data, which could have led to a possible selection bias. However, we did not observe any differences between excluded cases and PD cases with respect to baseline characteristics. By contrast to other studies, we thoroughly examined the interaction of anthropometric indices with smoking and PD. Despite having the highest number of PD-cases, restricting our analyses to "very likely" or "definite" cases limited the number of available cases substantially and more detailed sub-group analyses by a combination of sex, smoking history (e.g. time since quitting smoking and number of cigarettes smoked) and anthropometry were not possible, but would have probably shed some light on the complex associations with risk of PD. However, a descriptive analysis of the average number of cigarettes consumed in different smoking sub-groups, shows, that the mean and median are very similar among those groups. A limitation which should be considered while interpreting the results is that there might be other unconsidered and unknown confounding factors that have an influence on excess weight as well as PD. Also, it is important to note, that our follow-up time was probably not long enough and our sample size not large enough to exclude PD cases diagnosed within 15 years after baseline.

The literature on excess weight and risk of PD is inconsistent. Our large-scale, prospective analysis showed no association between elevated BMI or greater waist circumference and incident PD, which suggests, that body weight does not influence the risk of being diagnosed with PD in the next five to ten years. We detected a possible interaction by sex and smoking status at recruitment. While, among former or never smokers, an elevated BMI or waist circumference was not associated with risk of PD, overweight conferred a lower risk among smoking men but a greater risk among smoking women. Our obtained results suggest that associations between elevated BMI and PD may be driven by smoking status and that the combination of being overweight and smoking may trigger PD development differently in men and women. The possible interactions and our divergent findings merit further investigations in well-powered studies.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2019.01.019.

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