

1 **GENERAL AND ABDOMINAL ADIPOSITY AND THE RISK OF PARKINSON'S DISEASE:**
2 **A PROSPECTIVE COHORT STUDY**

3

4 **AUTHORS**

5 Lukas Riso¹, Rudolf Kaaks¹, Tilman Kühn¹, Disorn Sookthai¹, Lars Forsgren², Miles Trupp²,
6 Antonia Trichopoulou³, Carlo La Vecchia^{3,4}, Anna Karakatsani^{3,5}, Diana Gavrila^{6,7}, Pietro
7 Ferrari⁸, Heinz Freisling⁸, Jesper Petersson⁹, Susanne Lewan⁹, Roel CH Vermeulen^{10, 19},
8 Salvatore Panico¹¹, Giovanna Masala¹², Eva Ardanaz^{7,13,14}, Vittorio Krogh¹⁶, Robert G
9 Pernecky^{17,22,23}, Lefkos T Middleton¹⁷, Olatz Mokoroa¹⁸, Carlotta Sacerdote²⁰, Sabrina
10 Sieri¹⁶, Shabina A Hayat²¹, Carol Brayne²¹, Elio Riboli¹⁷, Paolo Vineis¹⁷, Valentina Gallo^{15,17},
11 Verena A Katzke^{1*}

12

13 **AFFILIATIONS**

14 ¹Division of Cancer Epidemiology, German Cancer Research Center (DKFZ), Germany

15 ²Department of Pharmacology and Clinical Neuroscience; Department of Biobank Research,
16 Umeå University, Sweden

17 ³Hellenic Health Foundation, Athens, Greece

18 ⁴Department of Clinical Sciences and Community Health Università degli Studi di Milano,
19 Italy

20 ⁵2nd Pulmonary Medicine Department, School of Medicine, National and Kapodistrian
21 University of Athens, "ATTIKON" University Hospital, Haidari, Greece

22 ⁶Department of Epidemiology, Murcia Regional Health Council, IMIB-Arrixaca, Murcia, Spain

23 ⁷CIBER Epidemiología y Salud Pública (CIBERESP), Spain

24 ⁸Nutritional Methodology and Biostatistics Group, International Agency for Research on
25 Cancer, Lyon, France

26 ⁹Department of Neurology, Lund University, Sweden

- 1 ¹⁰Julius Centre for Public Health Sciences and Primary Care, University Medical Centre,
2 Utrecht, The Netherlands
- 3 ¹¹Dipartimento di Medicina Clinica e Chirurgia Federico II Univeristy, Naples, Italy
- 4 ¹²Cancer Risk Factors and Life-Style Epidemiology Unit, Cancer Research and Prevention
5 Institute ISPO, Florence, Italy
- 6 ¹³Navarra Public Health Institute, Pamplona, Spain
- 7 ¹⁴IdiSNA, Navarra Institute for Health Research, Pamplona, Spain
- 8 ¹⁵Centre for Primary Care and Public Health, Blizard Institute, Queen Mary University of
9 London, London, UK
- 10 ¹⁶Epidemiology and Prevention Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan,
11 Italy
- 12 ¹⁷School of Public Health, Imperial College London, UK
- 13 ¹⁸Public Health and Addictions Directorate, Basque Government, Vitoria-Gasteiz,
14 BioDonostia Health Research Institute, Donostia-San Sebastian, Spain
- 15 ¹⁹Institute for Risk Assessment Science, Division of Epidemiology, Utrecht University,
16 Utrecht, The Netherlands
- 17 ²⁰Unit of Cancer Epidemiology, Città della Salute e della Scienza University-Hospital and
18 Center for Cancer Prevention (CPO), Turin, Italy
- 19 ²¹Department of Public Health and Primary Care, Institute of Public Health, University of
20 Cambridge, Cambridge, United Kingdom
- 21 ²²Department of Psychiatry and Psychotherapy, University Hospital, LMU Munich, Munich,
22 Germany
- 23 ²³German Center for Neurodegenerative Diseases (DZNE) Munich, Munich, Germany
- 24
- 25
- 26
- 27
- 28

1 ***Corresponding author:**

2 Verena A Katzke

3 Division of Cancer Epidemiology

4 German Cancer Research Center (DKFZ)

5 Im Neuenheimer Feld 581

6 69120 Heidelberg, Germany

7 +49 (0)6221-42 2363

8 v.katzke@dkfz.de

9

10

11 **KEYWORDS:**

12 Parkinson, Overweight, BMI, Smoking, Cohort, EPIC

13

1 ABSTRACT

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

6 Methods: In 13 of the 23 centers of the European Prospective Investigation into Cancer and
7 Nutrition (EPIC) study, a total of 734 incident cases of PD were identified between 1992 and
8 2012 with a mean follow-up of 12 years. Cox proportional hazards regression was used to
9 calculate hazard ratios (HR) with 95% confidence intervals (CI). We modelled anthropometric
10 variables as continuous and categorical exposures and performed subgroup analyses by
11 potential effect modifiers including sex and smoking.

12 Results: We found no association between BMI, WC and incident PD, neither among men
13 nor among women. Among never and former smokers, BMI and waist circumference were
14 also not associated with PD risk. For male smokers, however, we observed a statistically
15 significant inverse association between BMI and PD risk (HR 0.51, 95%CI: 0.30, 0.84) and
16 the opposite for women, i.e. a significant direct association of BMI (HR 1.79, 95%CI: 1.04,
17 3.08) and waist circumference (HR 1.64, 95%CI: 1.03, 2.61) with risk of PD.

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

20 INTRODUCTION

21 Parkinson's disease (PD) is the second most common late onset neurodegenerative disease,
22 following Alzheimer's Disease, with an incidence between 10 and 18 cases per 100,000
23 person-years [1-3]. Incidence rates are highest in (and post) the 7th decade with age being
24 the greatest risk factor for PD, while pathological changes preceding clinical symptomatology
25 typically occur already at the age of 50 [4]. The disease is generally more common among
26 men than among women [4]. Due to a rising life expectancy worldwide, the number of people

1 with PD are expected to appreciably increase in the near future [5]. Hence, development of
2 effective disease modifying therapies and identification of modifiable risk factors that would
3 allow primary prevention of PD are urgently needed [1, 2, 4]. While the precise biological
4 mechanisms underpinning the etiology of PD still remain unknown, the disease is thought to
5 result from complex interactions between genetic and environmental factors. A limited
6 number of risk factors beyond age and sex have already been discovered. Those include
7 rural living, agricultural occupation, pesticide exposure, well-water drinking, beta-blocker use,
8 and prior head injury [1]. Alcohol consumption, calcium channel blocker use, coffee
9 consumption and non-steroidal anti-inflammatory drug use have been associated with
10 relative risk reductions [1], and interestingly and most controversial, numerous epidemiologic
11 studies showed that tobacco smoking could also be a protective factor for PD [6-8]. The role
12 of excess body weight and its association with PD risk is still unclear [1, 9, 10].

13 The pathological hallmark of PD is a loss of dopaminergic neurons in the substantia nigra
14 pars compacta [1]. Of note, a decrement of dopamine - D₂ – receptor availability has been
15 reported in obese PD patients, in proportion to their body-mass-index (BMI) [11]. Obesity is
16 known to be pro-inflammatory; thus, obesity induced chronic inflammation may lead to higher
17 vulnerability to neurotoxins and/or increased neurotoxin levels and a decrease of dopamine
18 receptor availability, which may increase the risk of developing PD [12]. By contrast, a low
19 BMI has been associated with a decline in cognitive function in the elderly and has also been
20 suggested as a predictor for PD [13]. So far, excess BMI has been investigated as a risk
21 factor in several prospective cohort studies and summarized in two overlapping meta-
22 analyses [9, 10]. The latest meta-analysis based on 10 cohort studies did not find any
23 consistent association between obesity and PD [9]. Waist circumference, a surrogate for
24 visceral body fat, was not associated with risk of PD in two prospective investigations [14,
25 15].

26 These inconsistencies regarding the possible relationship between anthropometric indices of
27 adiposity and PD risk prompted us to examine the associations of two main anthropometric

1 indices with the future risk of PD, by sex and by smoking status, in a large European multi-
2 center population-based cohort.

3 METHODS

4 Study population

5 The current study is part of the population-based European Prospective Investigation into
6 Cancer and Nutrition (EPIC) study [16, 17]. The EPIC cohort consists of 519,978 participants
7 (366,521 men and 153,457 women), recruited between 1992 and 2000 in 23 centers across
8 10 European countries, mainly drawn at random from the general population with the
9 exception of Utrecht, where participants were part of a breast cancer screening program, and
10 Spain and Italy, where participants were recruited from the general population as well as
11 from selected enterprises and blood banks [17]. Thirteen of the 23 centers collected
12 information on neurodegenerative disorders at baseline during follow-up and formed the so
13 called NeuroEPIC4PD study, with the aim to investigate risk factors of neurodegenerative
14 disorders. The NeuroEPIC4PD study included 220,494 participants from the following 13
15 centers in 7 of the 10 European countries: Sweden (Umeå, Malmö), the Netherlands
16 (Utrecht), United Kingdom (Cambridge), Germany (Heidelberg), Spain (San Sebastian,
17 Navarra, Murcia), Italy (Turin, Varese, Florence, Naples), and Greece (countrywide). The
18 EPIC centers in Denmark, Norway and France were not included in the current study due to
19 unavailability of data on neurodegenerative disorders. A total of 137,174 of the
20 NeuroEPIC4PD cohort were women (62.2%) and 83,320 were men (37.8%) [16]. This study
21 was approved by local Ethical Committees. All participants signed a consent form for the use
22 of the obtained data.

23 Case ascertainment and sample size

24 To maximize sensitivity, potential PD cases were identified by each center via record linkage
25 with hospital records, hospital discharge files, outpatient/primary health care records, drug
26 prescription registries and/or mortality records (Umeå, Malmö, San Sebastian, Navarra,

1 Murcia), through active follow-up via self-reported questionnaires and/or interviews (Utrecht,
2 Greece) or both (Cambridge, Heidelberg, Turin, Varese, Florence, Naples) [16]. In this
3 process 1,723 potential cases of PD and Parkinson related diseases were identified and
4 their clinical records were reviewed by neurologists specialized in movement disorders [16].
5 Each case was either labeled as “definite”, “very likely”, “probable” or “possible”, based on
6 their likelihood of diagnosis which depended on the quality of data and the confidence of the
7 diagnosing neurologist (e.g. “definite” if the confidence of the neurologist was high and the
8 quality of data was excellent) [16]. Cases that failed to be labeled even as possible were not
9 qualified and were excluded from the analysis [16]. This led to overall 881 identified cases of
10 PD, 230 participants with parkinsonian-related disorders (e.g. multiple system atrophy) and
11 225 with unrelated conditions, while 387 potential cases were excluded because of missing
12 clinical data [16]. We subsequently excluded 147 prevalent PD cases at baseline, leaving a
13 total sample of 734 incident PD cases diagnosed between 1992 and 2012, with a mean
14 follow-up time of 12 years (range: 0-21) and, thus, a total of 220,347 participants. For a more
15 detailed description of case ascertainment methods we refer to Gallo et al. 2015 [16].

16 Lifestyle characteristics

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

1 were limited to 679 out of 734 cases. Details on anthropometric measurements in EPIC were
2 described elsewhere [18]. Body-Mass-Index (BMI) was used as an indicator for general
3 obesity and was calculated by dividing weight (in kilograms) by the square of height (in
4 meters). Waist circumference was analyzed as an indicator for central / abdominal obesity.

5 Statistical Analysis

6 Cox proportional hazards regression was used to calculate hazard ratios (HR) with 95%
7 confidence intervals (CI) with age as the time variable, PD as the outcome and adiposity
8 indices as the exposure variables. To account for death as a competing risk, we right-
9 censored our data at end of follow-up or death, whichever occurred first. All analyses were
10 performed for men and women separately to account for different PD prevalence by sex [4].
11 In the basic model, we adjusted for age at recruitment and center. We conducted a
12 multivariable adjusted model adjusted for age at recruitment, center, highest school level as
13 a proxy for socio-economic status, physical activity according to the Cambridge Physical
14 Activity Index [19] (inactive, moderately inactive, moderately active, active), coffee intake
15 (ml/day), alcohol consumption at recruitment (g/day) and in smokers additionally for age at
16 starting smoking, number of average lifetime cigarettes per day, lifetime duration of smoking,
17 smoking status at recruitment and time since quitting smoking (if never smoker). These
18 potential confounders have been discussed as possible risk factors of PD [1, 9, 20]. We
19 tested the validity of the proportional hazard assumption with Schoenfeld residuals. We
20 performed a continuous analysis where the HR referred to a change in BMI by 5 units and in
21 waist circumference by 10 units. In addition, we also performed categorical analyses using
22 pre-defined cut-points for BMI ($<25\text{kg/m}^2$, $25\text{-}30\text{kg/m}^2$, $\geq 30\text{kg/m}^2$ and $\leq 26\text{kg/m}^2$ vs.
23 $>26\text{kg/m}^2$ (median)) and waist circumference (men: $<94\text{cm}$, $94\text{-}102\text{cm}$, $\geq 102\text{cm}$; women:
24 $<80\text{cm}$, $80\text{-}88\text{cm}$, $\geq 88\text{cm}$). We did not specifically investigate underweight (BMI $<18.5\text{kg/m}^2$)
25 due to a limited number of PD cases (n=7) in that group. All analyses on waist circumference
26 were adjusted for height. Validity of the linearity assumption was tested by using restricted
27 cubic spline regression which did not show strong evidence of deviation from linearity in our

1 main model. Further, we conducted subgroup analyses by smoking status (never, former,
2 current). Heterogeneity by these suspected effect modifiers was assessed with Wald-
3 statistics. In addition, we conducted a Cox regression analysis of smoking status and PD risk
4 stratified by median BMI and median waist circumference to explore the complexity in the
5 triangle overweight – smoking – PD. We repeated the main analyses by restricting the
6 dataset to the “definite” and “very likely” diagnoses. To investigate possible reverse
7 causation, we excluded diagnosed cases within the first 5 and 10 years after baseline and
8 included cases diagnosed within 1 year prior to baseline. We did not adjust our significance
9 value of $p < 0.05$ for multiple testing because we only assessed two exposures and one
10 outcome with a total number of 16 performed analyses (excluding sensitivity analysis). All
11 statistical analyses were conducted using SAS, version 9.4 (SAS Institute, Cary, NC).

12 RESULTS

13 Main characteristics of our cohort are shown in **Table 1**. Although the NeuroEPIC4PD-cohort
14 included considerably more women (62%) than men (38%), numbers of PD cases in the
15 cohort were approximately equal between men ($n=378$; 51%) and women ($n=356$; 49%),
16 confirming the higher incidence of PD among men (cumulative incidence: 0.45% vs. 0.26%).
17 Mean age of study participants at baseline was 62 years (range 30-77) for cases and 53
18 years (range 19-86) for participants who did not develop PD, i.e. non-cases. Mean age of
19 onset of PD motor symptomatology was 70 (range 41-86) years in men and 69 (range 37-87)
20 in women. Participants who were diagnosed with PD during follow-up consumed less alcohol
21 and coffee at baseline than the comparison group of non-PD cases, irrespective of their sex.
22 Smoking at baseline was less common among men and women with later PD (14% and 8%,
23 respectively) than among the non-cases (29% and 22%, respectively).

24 *Associations of overweight with risk of PD*

25 Among men and women, neither BMI (per $5\text{kg}/\text{m}^2$, HR 0.86, 95%CI: 0.73, 1.01 and HR 1.01,
26 95%CI 0.88, 1.15, respectively) nor waist circumference (per 10cm, HR 1.01, 95%CI 0.89,
27 1.13 and HR 0.98, 95%CI 0.88, 1.10, respectively) were significantly associated with PD risk.

1 Using categorical instead of continuous variables resulted in comparable risk associations
2 **(Supplementary Tables 1 and 2).**

3 *Effect Modification by Smoking Status*

4 We observed heterogeneity by smoking status (never vs. current) in the association between
5 BMI and PD risk (men: $p\text{-het} < 0.001$, women: $p\text{-het} = 0.05$) (**Table 2**). Among never and former
6 smokers, neither BMI nor waist circumference were significantly associated with PD risk.
7 Among current smokers at baseline, BMI was inversely associated with risk of PD among
8 men (HR 0.51, 95%CI: 0.30, 0.84), in contrast to a direct association in women (HR 1.79,
9 95%CI: 1.04, 3.08, $p\text{-het} < 0.001$ between men and women among current smokers).
10 Associations in similar magnitude were also observed for waist circumference among
11 smoking women (HR 1.64, 95%CI: 1.03, 2.61) but not men.

12 *Exploratory Analyses Smoking – BMI*

13 To further elucidate these complex interactions, we alternatively examined the associations
14 of smoking status with PD risk by strata of BMI (**Supplementary Table 3**). In this analysis,
15 current compared to never smoking was inversely associated with PD risk (HR 0.40, 95%CI:
16 0.24, 0.66) among men with a BMI above 26kg/m^2 , but not among men with $\text{BMI} \leq 26\text{kg/m}^2$
17 (median). In contrast, an inverse association of current smoking with PD risk was observed in
18 leaner ($\text{BMI} \leq 26\text{kg/m}^2$; (HR 0.36, 95%CI: 0.19, 0.66), but not in more obese women.

19 *Sensitivity Analyses*

20 Exclusion of PD cases that were diagnosed within the first five or ten years (data for 10 years
21 not shown) after baseline and inclusion of cases diagnosed within 1 years prior to baseline
22 did either not or only marginally influence any association between anthropometric measures
23 and risk of PD. The only exceptions are the associations of BMI and waist circumference with
24 risk of PD among smoking women, where risk estimates became even stronger after the
25 exclusion of those cases that were diagnosed within 5 years after baseline (**Table 2**).
26 Restricting the analysis to cases with the aforementioned diagnosis probability labeled as

1 “very likely” or “definite” (n=397) did not result in significant associations of BMI or waist
2 circumference with PD risk, irrespective of the participant’s smoking status (**Table 2**).

3 DISCUSSION

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

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

23 Smoking status as an effect modifier was only investigated in one of these studies but
24 without a differentiation between current and former smokers and with no evident interaction
25 [21]. The more recent study did not account for a possible effect modification by smoking
26 history although there was evidence of an unadjusted difference in mean BMI (BMI among

1 never and past smokers: 27.2kg/m², BMI among smokers: 25.0kg/m²) [22]. While cohorts of
2 both studies were small (n=45,806 and n=6,715) compared to our cohort (n=220,494), they
3 included a very high number of cases (n=526 and n=101), which is most likely the
4 consequence of their longer average follow-up times (19 years and 22 years), as compared
5 to 12 years in the present dataset. These study characteristics may explain the divergent
6 findings between the Finnish cohorts and ours. A long follow-up may increase the likelihood
7 of people changing their smoking habits and their weight prior of a possible PD diagnosis,
8 resulting in biased risk estimates that rely on baseline assessments. However, these are
9 mere speculations and the reasons for the divergent results remain unclear. A recently
10 published Mendelian randomization study with 13,708 cases of PD found an inverse
11 association of BMI with the risk of PD (OR 0.82, 95%CI: 0.69, 0.98) [23]. However, the
12 analysis by strata of smoking status could not be performed on aggregated data and, thus,
13 the possibility that their observed association may be largely driven by the strong interaction
14 between smoking status, BMI and sex could not be assessed.

15 In our study, waist circumference was associated with a 1.6-fold higher PD risk in smoking
16 women but not in men or non-smokers, suggesting that the location of body fat in
17 combination with smoking status might have an influence on risk of PD depending on
18 individuals' sex. By contrast, Chen et al. 2004 observed in two US cohorts no association
19 between waist circumference and PD risk among ever smokers (i.e. smokers and former
20 smokers) but a direct association in a comparable magnitude among never smoking men
21 and women combined [14]. Palacios et al. 2011 conducted an analysis stratified by smoking
22 status and found no association between waist circumference and PD risk, neither among
23 never smokers nor among ever smokers in a further US cohort [15]. In contrast to our study
24 where measurement of the majority of anthropometric indices was performed by trained
25 observers, all three studies relied on self-reported and self-measured data on waist
26 circumference [14, 15]. The studies did not differentiate between former and current smokers
27 [14, 15], thus, a possible difference between those two groups could not be investigated.

1 Obesity has been controversially discussed in regards to its biological impact on PD: on the
2 one hand possibly increasing the risk by decreasing the availability of dopamine receptors and
3 increasing the vulnerability to neurotoxins [12], on the other hand leaner subjects tend to have
4 a higher risk of cognitive decline [13] and PD patients gaining weight following deep brain
5 stimulation [24]. The difference in prevalence between men and women led to the idea that
6 estrogen might have a protective effect on PD [25]. Smoking has been described as a
7 protective factor against PD [6] by weakening the effect of different neurotoxins and
8 improving the dopamine effect in both sexes [26] which is consistent with our data (overall
9 HR for current smokers compared to never smokers 0.49, 95%CI: 0.38, 0.63 [27]).
10 Paradoxically, we found that in men smoking was associated with reduced PD risk only for
11 those who were overweight (BMI >26kg/m²), whilst in women this association was observed
12 only for those who were comparably leaner (BMI ≤26kg/m²), which clarifies, why we did not
13 see any strong inverse association in the continuous model with an elevated BMI among
14 smoking women. However, one has to bear in mind that number of overweight women who
15 smoked and developed PD during follow-up was small with 17 in total. The possible
16 interaction between smoking, BMI and sex may, indeed, result from a complex interplay of
17 competing risks (primarily death such as in the subgroup of smoking men, where the inverse
18 association between BMI and PD could be due to early deaths of overweight smoking men),
19 hormones, as well as long-term effects of heavy smoking on body composition; for instance,
20 it has been reported that sub-groups of long-term, heavy smokers are characterized by
21 extreme leanness [28]. Also, time from cessation of smoking can impact time spent
22 overweight, and therefore duration of adipose related inflammation. There are no obvious
23 plausible biological explanations for the divergent results and they are subject to speculation.
24 Is adiposity influencing the complex protective effect of smoking on PD risk depending on
25 sex and, hence, individuals' hormone status? Our sensitivity analysis and the lack of
26 association between waist circumference and PD risk among male smokers show that they
27 need to be interpreted with caution. Further investigations in well-powered studies including

1 biomarker assessments are necessary to not only verify our results but also to unravel the
2 biological nature of the associations.

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

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

26 The literature on excess weight and risk of PD is inconsistent. Our large-scale, prospective
27 analysis showed no association between elevated BMI or greater waist circumference and

1 incident PD, which suggests, that body weight does not influence the risk of being diagnosed
2 with PD in the next five to ten years. We detected a possible interaction by sex and smoking
3 status at recruitment. While, among former or never smokers, an elevated BMI or waist
4 circumference was not associated with risk of PD, overweight conferred a lower risk among
5 smoking men but a greater risk among smoking women. Our obtained results suggest that
6 associations between elevated BMI and PD may be driven by smoking status and that the
7 combination of being overweight and smoking may trigger PD development differently in men
8 and women. The possible interactions and our divergent findings merit further investigations
9 in well-powered studies.

10

11 FUNDING / ACKNOWLEDGEMENTS

12 This research has been made possible thanks to a grant of the European Community (5th
13 Framework Programme) to Prof. Paolo Vineis (grant QLK4CT199900927); and a grant of the
14 Compagnia di San Paolo to the ISI Foundation. All authors are independent from founders.
15 Mortality data from the Netherlands are obtained from "Statistics Netherlands". The centers
16 contributing to the NeuroEPIC4PD study are financially supported by: Europe Against
17 Cancer Program of the European Commission (SANCO); ISCIII, Red de Centros RCESP,
18 C03/09; Spanish Ministry of Health (ISCIII RETICC RD06/0020); German Cancer Aid;
19 German Cancer Research Center (DKFZ); German Federal Ministry of Education and
20 Research (BMBF); Danish Cancer Society; Health Research Fund (FIS) of the Spanish
21 Ministry of Health; Spanish Regional Governments of Andalucia, Asturias, Basque Country,
22 Murcia and Navarra; Spanish Ministry of Health (ISCIII RETICC RD06/0020) Cancer
23 Research U.K.; Medical Research Council, United Kingdom; Stroke Association, United
24 Kingdom; British Heart Foundation; Department of Health, United Kingdom; Food Standards
25 Agency, United Kingdom; Welcome Trust, United Kingdom Greek Ministry of Health; Greek
26 Ministry of Education; Italian Association for Research on Cancer (AIRC); Italian National
27 Research Council; Dutch Ministry of Public Health, Welfare and Sports (VWS); Netherlands

1 Cancer Registry (NKR); LK Research Funds; Dutch Prevention Funds, Dutch ZON (Zorg
2 Onderzoek Nederland); World Cancer Research Fund (WCRF); Statistics Netherlands (The
3 Netherlands); Swedish Cancer Foundation; Swedish Scientific Council; Regional
4 Governments of Skåne and Västerbotten Counties, Sweden; Norwegian Cancer Society;
5 Research Council of Norway; French League against cancer, Inserm, Mutuelle Generale
6 l'Education National and IGR; the Hellenic Health Foundation.
7

1 REFERENCES

- 2
- 3 [1] L.V. Kalia, A.E. Lang, Parkinson's disease, *Lancet* 386(9996) (2015) 896-912.
- 4 [2] S. von Campenhausen, B. Bornschein, R. Wick, K. Botzel, C. Sampaio, W. Poewe, W. Oertel, U.
5 Siebert, K. Berger, R. Dodel, Prevalence and incidence of Parkinson's disease in Europe, *Eur*
6 *Neuropsychopharmacol* 15(4) (2005) 473-90.
- 7 [3] S.K. Van Den Eeden, C.M. Tanner, A.L. Bernstein, R.D. Fross, A. Leimpeter, D.A. Bloch, L.M. Nelson,
8 Incidence of Parkinson's disease: variation by age, gender, and race/ethnicity, *Am J Epidemiol*
9 157(11) (2003) 1015-22.
- 10 [4] L.M. de Lau, M.M. Breteler, Epidemiology of Parkinson's disease, *Lancet Neurol* 5(6) (2006) 525-
11 35.
- 12 [5] E.R. Dorsey, R. Constantinescu, J.P. Thompson, K.M. Biglan, R.G. Holloway, K. Kieburtz, F.J.
13 Marshall, B.M. Ravina, G. Schifitto, A. Siderowf, C.M. Tanner, Projected number of people with
14 Parkinson disease in the most populous nations, 2005 through 2030, *Neurology* 68(5) (2007) 384-6.
- 15 [6] M.A. Hernan, B. Takkouche, F. Caamano-Isorna, J.J. Gestal-Otero, A meta-analysis of coffee
16 drinking, cigarette smoking, and the risk of Parkinson's disease, *Ann Neurol* 52(3) (2002) 276-84.
- 17 [7] X. Li, W. Li, G. Liu, X. Shen, Y. Tang, Association between cigarette smoking and Parkinson's
18 disease: A meta-analysis, *Arch Gerontol Geriatr* 61(3) (2015) 510-6.
- 19 [8] M.F. Allam, M.J. Campbell, A. Hofman, A.S. Del Castillo, R. Fernandez-Crehuet Navajas, Smoking
20 and Parkinson's disease: systematic review of prospective studies, *Mov Disord* 19(6) (2004) 614-21.
- 21 [9] Y.L. Wang, Y.T. Wang, J.F. Li, Y.Z. Zhang, H.L. Yin, B. Han, Body Mass Index and Risk of Parkinson's
22 Disease: A Dose-Response Meta-Analysis of Prospective Studies, *PLoS One* 10(6) (2015) e0131778.
- 23 [10] J. Chen, Z. Guan, L. Wang, G. Song, B. Ma, Y. Wang, Meta-analysis: overweight, obesity, and
24 Parkinson's disease, *Int J Endocrinol* 2014 (2014) 203930.
- 25 [11] G.J. Wang, N.D. Volkow, J. Logan, N.R. Pappas, C.T. Wong, W. Zhu, N. Netusil, J.S. Fowler, Brain
26 dopamine and obesity, *Lancet* 357(9253) (2001) 354-7.
- 27 [12] H. Ashrafian, L. Harling, A. Darzi, T. Athanasiou, Neurodegenerative disease and obesity: what is
28 the role of weight loss and bariatric interventions?, *Metab Brain Dis* 28(3) (2013) 341-53.
- 29 [13] H.J. Kim, E.S. Oh, J.H. Lee, J.S. Moon, J.E. Oh, J.W. Shin, K.J. Lee, I.C. Baek, S.H. Jeong, H.J. Song,
30 E.H. Sohn, A.Y. Lee, Relationship between changes of body mass index (BMI) and cognitive decline in
31 Parkinson's disease (PD), *Arch Gerontol Geriatr* 55(1) (2012) 70-2.
- 32 [14] H. Chen, S.M. Zhang, M.A. Schwarzschild, M.A. Hernan, W.C. Willett, A. Ascherio, Obesity and
33 the risk of Parkinson's disease, *Am J Epidemiol* 159(6) (2004) 547-55.
- 34 [15] N. Palacios, X. Gao, M.L. McCullough, E.J. Jacobs, A.V. Patel, T. Mayo, M.A. Schwarzschild, A.
35 Ascherio, Obesity, diabetes, and risk of Parkinson's disease, *Mov Disord* 26(12) (2011) 2253-9.
- 36 [16] V. Gallo, C. Brayne, L. Forsgren, R.A. Barker, J. Petersson, O. Hansson, D. Lindqvist, C. Ruffmann,
37 L. Ishihara, R. Luben, L. Arriola, A. Bergareche, D. Gavrila, M.E. Erro, N. Vanacore, C. Sacerdote, B.
38 Bueno-de-Mesquita, R. Vermeulen, M. Seelen, S. Sieri, G. Masala, S. Ramat, A. Kyrozi, A.
39 Thricopolou, S. Panico, A. Mattiello, R. Kaaks, B. Teucher, V. Katzke, M. Kloss, L. Curry, F. Calboli, E.
40 Riboli, P. Vineis, L. Middleton, Parkinson's Disease Case Ascertainment in the EPIC Cohort: The
41 NeuroEPIC4PD Study, *Neurodegener Dis* 15(6) (2015) 331-8.
- 42 [17] E. Riboli, K.J. Hunt, N. Slimani, P. Ferrari, T. Norat, M. Fahey, U.R. Charrondiere, B. Hemon, C.
43 Casagrande, J. Vignat, K. Overvad, A. Tjonneland, F. Clavel-Chapelon, A. Thiebaut, J. Wahrendorf, H.
44 Boeing, D. Trichopoulos, A. Trichopoulou, P. Vineis, D. Palli, H.B. Bueno-De-Mesquita, P.H. Peeters, E.
45 Lund, D. Engeset, C.A. Gonzalez, A. Barricarte, G. Berglund, G. Hallmans, N.E. Day, T.J. Key, R. Kaaks,
46 R. Saracci, European Prospective Investigation into Cancer and Nutrition (EPIC): study populations
47 and data collection, *Public Health Nutr* 5(6B) (2002) 1113-24.
- 48 [18] M. Haftenberger, P.H. Lahmann, S. Panico, C.A. Gonzalez, J.C. Seidell, H. Boeing, M.C.
49 Giurdanella, V. Krogh, H.B. Bueno-de-Mesquita, P.H. Peeters, G. Skeie, A. Hjartaker, M. Rodriguez,
50 J.R. Quiros, G. Berglund, U. Janlert, K.T. Khaw, E.A. Spencer, K. Overvad, A. Tjonneland, F. Clavel-
51 Chapelon, B. Tehard, A.B. Miller, K. Klipstein-Grobusch, V. Benetou, G. Kiriazi, E. Riboli, N. Slimani,
52 Overweight, obesity and fat distribution in 50- to 64-year-old participants in the European
53 Prospective Investigation into Cancer and Nutrition (EPIC), *Public Health Nutr* 5(6B) (2002) 1147-62.

- 1 [19] N.J. Wareham, R.W. Jakes, K.L. Rennie, J. Mitchell, S. Hennings, N.E. Day, Validity and
2 repeatability of the EPIC-Norfolk Physical Activity Questionnaire, *Int J Epidemiol* 31(1) (2002) 168-74.
- 3 [20] V. Bellou, L. Belbasis, I. Tzoulaki, E. Evangelou, J.P. Ioannidis, Environmental risk factors and
4 Parkinson's disease: An umbrella review of meta-analyses, *Parkinsonism Relat Disord* 23 (2016) 1-9.
- 5 [21] G. Hu, P. Jousilahti, A. Nissinen, R. Antikainen, M. Kivipelto, J. Tuomilehto, Body mass index and
6 the risk of Parkinson disease, *Neurology* 67(11) (2006) 1955-9.
- 7 [22] K. Saaksjarvi, P. Knekt, S. Mannisto, J. Lyytinen, T. Jaaskelainen, N. Kanerva, M. Heliovaara,
8 Reduced risk of Parkinson's disease associated with lower body mass index and heavy leisure-time
9 physical activity, *Eur J Epidemiol* 29(4) (2014) 285-92.
- 10 [23] A.J. Noyce, D.A. Kia, G. Hemani, A. Nicolas, T.R. Price, E. De Pablo-Fernandez, P.C. Haycock, P.A.
11 Lewis, T. Foltynie, G. Davey Smith, C. International Parkinson Disease Genomics, A. Schrag, A.J. Lees,
12 J. Hardy, A. Singleton, M.A. Nalls, N. Pearce, D.A. Lawlor, N.W. Wood, Estimating the causal influence
13 of body mass index on risk of Parkinson disease: A Mendelian randomisation study, *PLoS Med* 14(6)
14 (2017) e1002314.
- 15 [24] I. Rieu, P. Derost, M. Ulla, A. Marques, B. Debilly, I. De Chazeron, I. Chereau, J.J. Lemaire, Y.
16 Boirie, P.M. Llorca, F. Durif, Body weight gain and deep brain stimulation, *J Neurol Sci* 310(1-2) (2011)
17 267-70.
- 18 [25] R. Saunders-Pullman, Estrogens and Parkinson disease: neuroprotective, symptomatic, neither,
19 or both?, *Endocrine* 21(1) (2003) 81-7.
- 20 [26] M. Quik, X.A. Perez, T. Bordia, Nicotine as a potential neuroprotective agent for Parkinson's
21 disease, *Mov Disord* 27(8) (2012) 947-57.
- 22 [27] V. Gallo, P. Vineis, M. Cancellieri, P. Chiodini, R.A. Barker, C. Brayne, N. Pearce, R. Vermeulen, S.
23 Panico, B. Bueno-de-Mesquita, N. Vanacore, L. Forsgren, S. Ramat, E. Ardanaz, L. Arriola, J. Peterson,
24 O. Hansson, D. Gavrila, C. Sacerdote, S. Sieri, T. Kuhn, V.A. Katzke, Y.T. van der Schouw, A. Kyrozi, G.
25 Masala, A. Mattiello, R. Pernecky, L. Middleton, R. Saracci, E. Riboli, Exploring causality of the
26 association between smoking and Parkinson's disease, *Int J Epidemiol* (2018).
- 27 [28] G. Wannamethee, A.G. Shaper, Body weight and mortality in middle aged British men: impact of
28 smoking, *BMJ* 299(6714) (1989) 1497-502.

29