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Caffeine Exposure and the Risk of Parkinson's Disease: A Systematic Review and Meta-Analysis of Observational Studiess

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Abstract. Several studies conducted worldwide report an inverse association between caffeine/coffee consumption and the risk of developing Parkinson's disease (PD). However, heterogeneity and conflicting results between studies preclude a correct estimation of the strength of this association. We conducted a systematic review and meta-analysis of published epidemiological studies to better estimate the effect of caffeine exposure on the incidence of PD. Data sources searched included Medline, LILACS, Scopus, Web of Science and reference lists, up to September 2009. Cohort, case-control and cross-sectional studies were included. Three independent reviewers selected the studies and extracted the data on to standardized forms. Twenty-six studies were included: 7 cohort, 2 nested case-control, 16 case-control, and 1 cross-sectional study. Quantitative data synthesis of the most precise estimates from each study was accomplished through random effects meta-analysis. Heterogeneity was quantified using the I^2 statistic. The summary RR for the association between caffeine intake and PD was 0.75 [95% Confidence Interval (95%CI): 0.68–0.82], with low to moderate heterogeneity ($I^2 = 28.8\%$). Publication bias for case-control/cross-sectional studies may exist (Egger's test, $p = 0.053$). When considering only the cohort studies, the RR was 0.80 (95%CI: 0.71–90; $I^2 = 8.1\%$). The negative association was weaker when only women were considered (RR = 0.86, 95%CI: 0.73–1.02; $I^2 = 12.9\%$). A linear relation was observed between levels of exposure to caffeine and the RR estimates: RR of 0.76 (95%CI: 0.72–0.80; $I^2 = 35.1\%$) per 300 mg increase in caffeine intake. This study confirm an inverse association between caffeine intake and the risk of PD, which can hardly by explained by bias or uncontrolled confounding.

Keywords: Caffeine, meta-analysis, Parkinson's disease, relative risk, risk assessment

INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disease with an estimated worldwide prevalence of 0.5 to 4% among the elderly [1]. The underlying neuropathological lesion is the degeneration of the pigmented neurons of the substantia nigra, locus caeruleus, and other brain stem dopaminergic cell groups, with the subsequent loss of dopaminergic neurons terminals in the striatum. The continuous depletion of dopamine is responsible for most of the debilitating motor disturbances of the disease. The cardinal signs include bradykinesia, rigidity, rest tremor, gait disturbances, and postural instability [2].

There is not a single cause of PD, and multiple etiological factors with complex interactions are thought to be responsible for the development and progression of the disease [3,4]. The results of genetic and epidemiological studies suggest that genetic factors are particularly important in early-onset cases of PD [5,6] while the environmental component is probably more

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relevant in the development of PD at older ages (above 50 years) [1].

There is a long list of environmental and lifestyle factors that have been associated with PD, either as risk or protective factors for the development of the disease. Infections, place of birth at early life, drinking well-water, occupational exposure to welding, heavy metals or pesticides, and lack of vigorous exercise have all been referred to in the literature as putative risk factors [7–12]. On the other hand, smoking and consumption of coffee, tea, or nonsteroidal anti-inflammatory drugs are thought as possible protective factors [13]. Among all these factors, the most well studied in the literature are cigarette smoking and lifetime coffee consumption. In fact, the associations between smoking and coffee and lower risk of PD were first mentioned in the literature many years ago [14,15]. Since then, several large epidemiological studies conducted in the US, Europe, and Asia reported a dose-dependent inverse association between exposure to these factors and the risk of developing PD. These inverse associations were corroborated in family-based case-control studies, thus emphasizing smoking and caffeine as important covariates in any genetic or epidemiological studies of PD [16].

The strength of the evidence for the described inverse associations is weaker for coffee/caffeine than for smoking, because there are fewer studies and the magnitude of the effect is lower. A meta-analysis by Hernán and colleagues, published 8 years ago, found a polled relative risk of PD of about 60% and 30% lower among smokers and coffee drinkers in comparison to nonsmokers and non-coffee drinkers, respectively [17]. These results were based on a large number of studies (44 case-control and 4 cohort studies) for the smoking association, but on only 13 studies (8 case-control and 5 cohort studies) for coffee drinking. In addition, there is heterogeneity between studies results, and some of the studies published since then failed to show a significant negative association [18–21] or suggested significant differences between men and women, especially postmenopausal women on estrogen replacement therapy [22,23]. There are also conflicting findings in the few available data about the putative association of caffeine and the rate of progression of PD or the age of motor symptoms onset. Recent studies failed to identify any consistent relation either with the rate of progression [24,25] or the age of motor symptoms onset [26, 27].

In view of the results of these more recent studies, we conducted a systematic review and a meta-analysis of the literature to quantify the association between caffeine intake and PD.

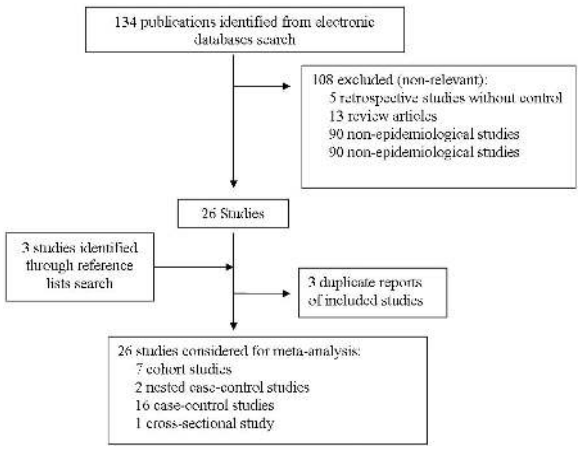

Fig. 1. Systematic review flow-chart.

MATERIALS AND METHODS

Search strategy and selection criteria

Potential eligible studies were identified through an electronic search of the databases Medline, LILACS (Latin America and Caribbean), Scopus and Web of Science (Fig. 1). The latest search of these databases was performed on September 2009. The search strategy for Medline combined the terms (coffee OR caffeine) with (Parkinson or Parkinson disease) together with a search filter developed for the retrieval of epidemiological studies (Cohort Studies OR Case Control Studies OR Prospective Studies OR Follow-Up Studies OR Cross-Sectional Studies OR Retrospective studies OR Epidemiological OR Incidence OR Risk Factors OR Risk Assessment OR Risk Reduction OR Relative Risk OR Behavior Regression Analysis OR Multivariate Analysis OR Proportional Hazards Models). All terms were searched as MeSH (Medical Subjects Headings) and free-text words. Moreover, the reference lists of relevant studies were cross-checked for potential additional studies not identified by the electronic search. We screened titles, keywords, and abstracts and obtained full copies of potentially suitable reports. There were no language restrictions and reports published as a full paper or abstract were considered as long as relevant data could be extracted.

The studies with cohort, case-control or cross-sectional designs that evaluated the relation between exposure to coffee/caffeine and the risk of PD (all diagnostic criteria were considered) or PD mortality were eligible for the systematic review. We excluded studies addressing the effects of short-term exposure to coffee

or caffeine and those that evaluated associations other than the risk of PD, such as the rate of progression. No studies were excluded *a priori* for weakness of design or data quality.

Data extraction

Three authors independently assessed the identified studies (JC, JS, and CS). Study details were obtained independently, written on predefined standardized forms, and cross checked for accuracy. Disagreements were resolved by consensus after repeated examination of the articles.

The information abstracted included the study characteristics (publication year, country of origin, study period, study design and length of follow-up), participant characteristics (number, age and gender), selection of cases and controls in case-control studies, assessment of coffee/caffeine intake and outcome (criteria for definition of PD or PD mortality), adjustment for potential confounders, and estimates of the association between different measures of coffee/caffeine exposure and PD.

When different risk estimates were available in the same publication, we opted for those that reflected the greatest degree of control for potential confounder, to the largest number of categories of exposure among caffeine consumers, or to the most comprehensive assessment of caffeine intake, applying these criteria consecutively. If results were provided separately for different caffeine-containing beverages or food items we opted for those referring to coffee consumption. Stratum-specific Relative Risk (RR) estimates [according to gender, use of Hormonal Replacement Therapy (HRT), or genetic polymorphisms related to caffeine metabolization] were extracted whenever available. Ross and colleagues [28] provided adjusted RRs but the highest category of exposure was used as reference and crude RR estimates were computed using the lowest exposure as reference. The crude estimates, however, were not meaningfully different from the adjusted ones. Ascherio and coworkers [29] provided RR estimates for both coffee and caffeine intake. The latter was provided graphically and the former was extracted, but there were no meaningful differences in the RR estimates per exposure level for coffee and caffeine.

Three studies [15,30,31] had matched case-control designs and did not provide Odds Ratio (OR) estimates for the association between caffeine intake and PD, or the data necessary for the calculation of valid estimates. Since the OR for drinkers vs. non-drinkers computed using information from these studies is available in the meta-analysis by Hérnan et al. [17], which reported to have contacted the authors for additional information, we used the estimates they computed. Haack and collaborators [32] provided the OR for drinkers vs. non-drinkers in their report but it is slightly different from the provided by Hérnan et al. [17] and we used the latter in our meta-analyses.

When there was more than one publication for the same study, we used the one providing more detailed information on the relation between coffee/caffeine intake and PD, using the same criteria applied when more than one estimate was available from the same study, or referring to the longer follow-up (for cohort designs).

The samples evaluated by Ascherio and colleagues in 2001 [29] and in 2003 [33] overlap partially and we used the results referring to males presented in the study published in 2001, as these are not available in the 2003 study, and the results referring to females published in 2003.

Data synthesis

Each study is summarized in Table 1 and Fig. 2. The forest plot corresponding to Fig. 2 represents the RR estimates provided in each study for the association between caffeine intake and PD. Several estimates from the same study may be provided, referring to different exposure levels or to stratum-specific analyses.

Quantitative data synthesis was accomplished through random effects meta-analysis (DerSimonian and Laird method) (Fig. 3). Relative risks (cumulative incidence ratios or incidence density ratios) and ORs were treated the same and are referred to as RR. A cumulative random effects meta-analysis (Fig. 4) was conducted to allow a better understanding of the time trends in the understanding of the relation between caffeine intake and PD.

Summary estimates for exposure to caffeine were computed considering the individual RR estimates corresponding to coffee, coffee, and tea or caffeine intake (from caffeinated beverages or caffeinated beverages and chocolate), as available from each article, under the assumption that coffee is the main contributor for caffeine intake.

Since more than one RR estimate was available from several studies, only the most precise measures of association were used from each report (except for stratum-specific estimates, which were considered separately as if obtained from different studies). This criterion was followed for selection of a single estimate per study

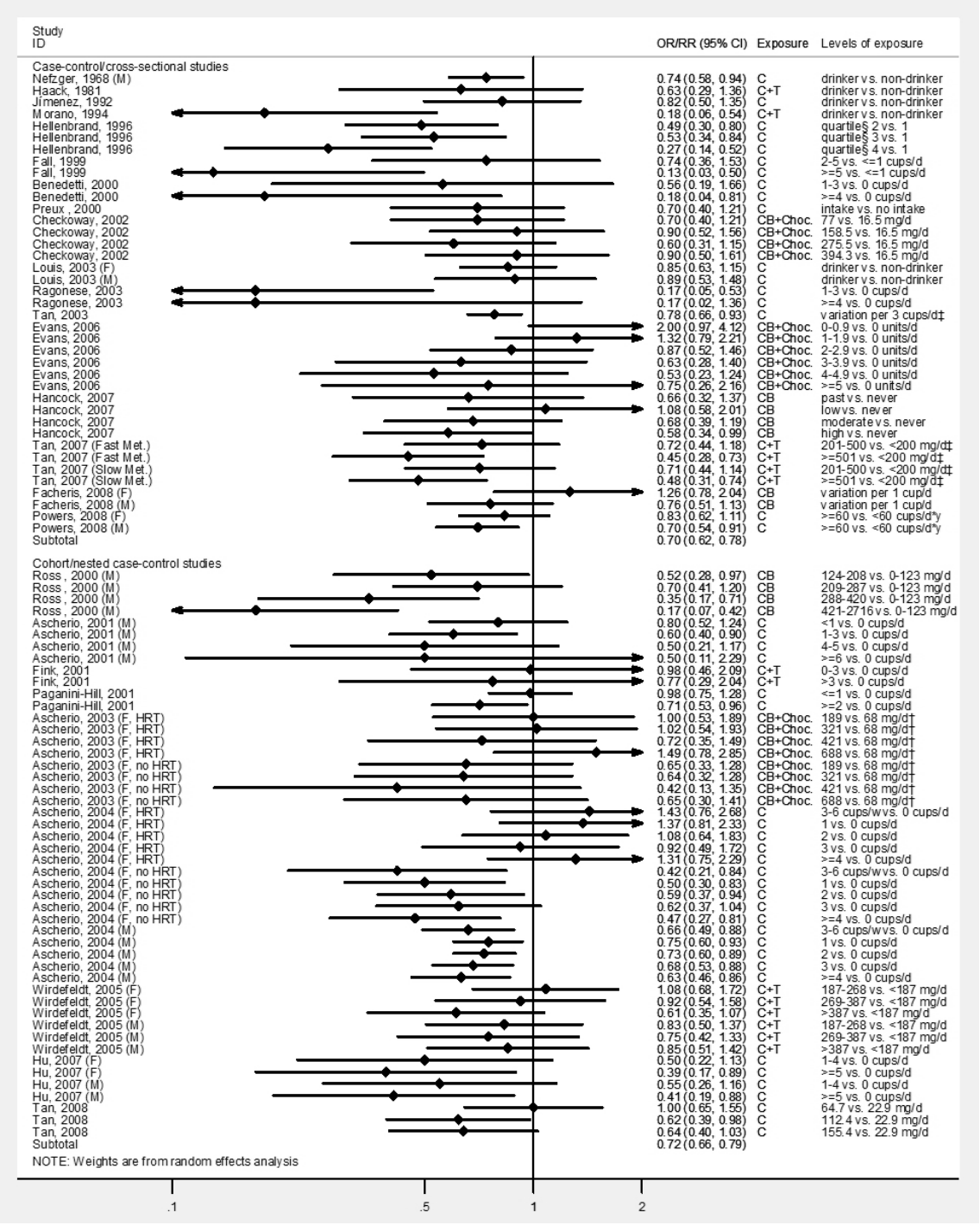

Fig. 2. Relative Risk estimates for the association between caffeine and Parkinson's disease, according to sources of caffeine intake and levels of exposure. Legend: ID – Identification; OR/RR – Odds Ratio/Relative Risk; M – Male; F – Female; C – coffee; T – tea; C+T – coffee and tea; CB – caffeinated beverages; CB+Choc. – caffeinated beverages and chocolate; Fast Met. – Fast metabolizers; Slow Met. – Slow metabolizers; HRT – Hormonal Replacement Therapy; d – day; w – week; † – the exposures correspond to the median of each fifth of the distribution; ‡ – consumption in mg/day for 10 years; § – levels of exposure not further specified

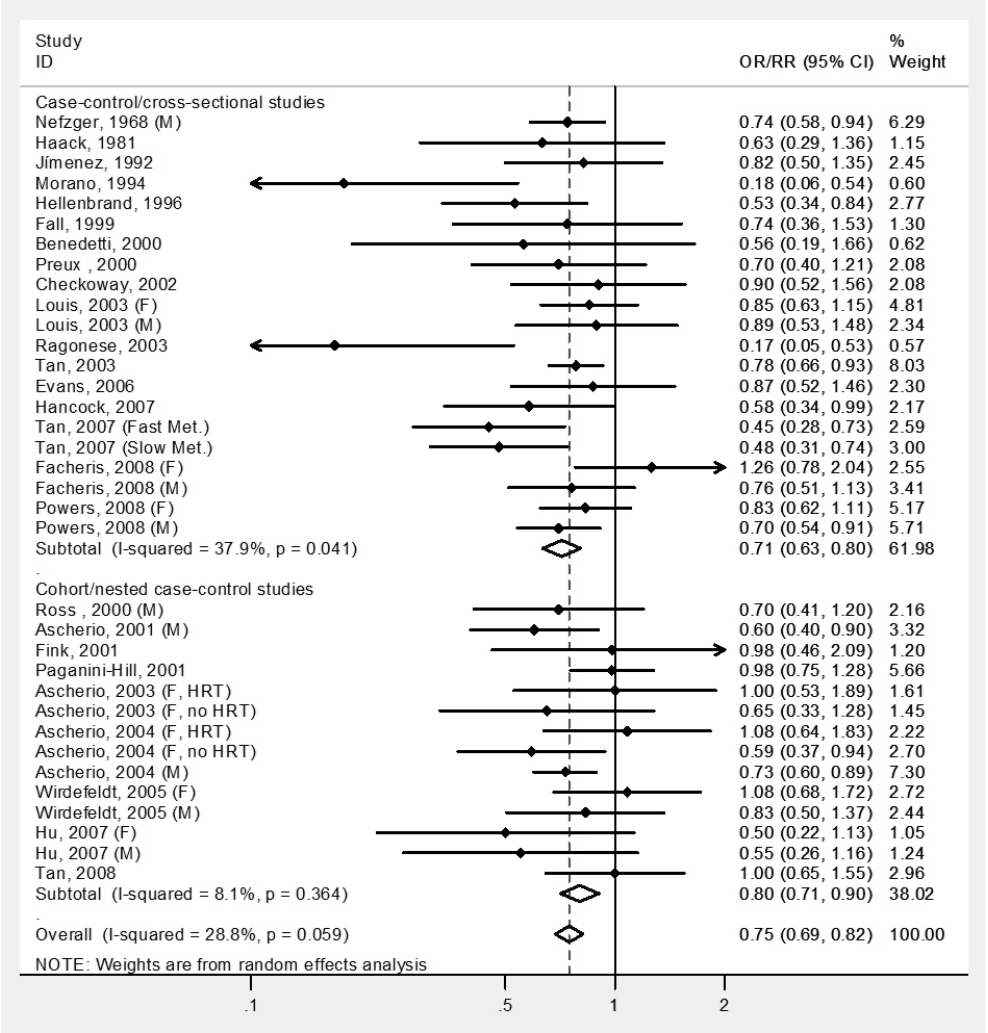

Fig. 3. Meta-analysis for the association between caffeine and Parkinson's disease, including the most precise RR estimates from each individual study. Legend: ID – Identification; OR/RR – Odds Ratio/Relative Risk; M – Male; F – Female; Fast Met. – Fast metabolizers; Slow Met. – Slow metabolizers; HRT – Hormonal Replacement Therapy.

when RRs were provided for different categories of exposure. If the precision of RR estimates was the same for more than one category we conservatively chose the one corresponding to the RR closest to 1.

The dose response relation between caffeine intake and PD was assessed through visual inspection of a scatter plot representing the RR estimates from each study (in a log scale) according to the exposure to caffeine (Fig. 5), and quantified by weighted least squares regression (WLS). All the RR estimates (for each level of exposure and for each stratum-specific analysis) obtained from studies providing RR estimates for at least two categories of exposure compared with the referent were plotted and included in the regression model. This information was obtained from 15 studies [19,20, 22,23,26,28,29,33–40], corresponding to 69 RR estimates. The exposures corresponding to each RR estimate were those provided by the authors (e.g. median of each distribution quantile) or assumed to correspond to the midpoint of each index category range subtracted by the midpoint of the reference category range. For this purpose, we assumed that the open-ended upper category had the amplitude of the preceding stratum. The caffeine intake corresponding to each category of exposure or the information to compute it was provided by most studies. For three studies conducted in the USA [22,26,36] we assumed that a cup of coffee corresponds to 137 mg of caffeine (based on the estimates

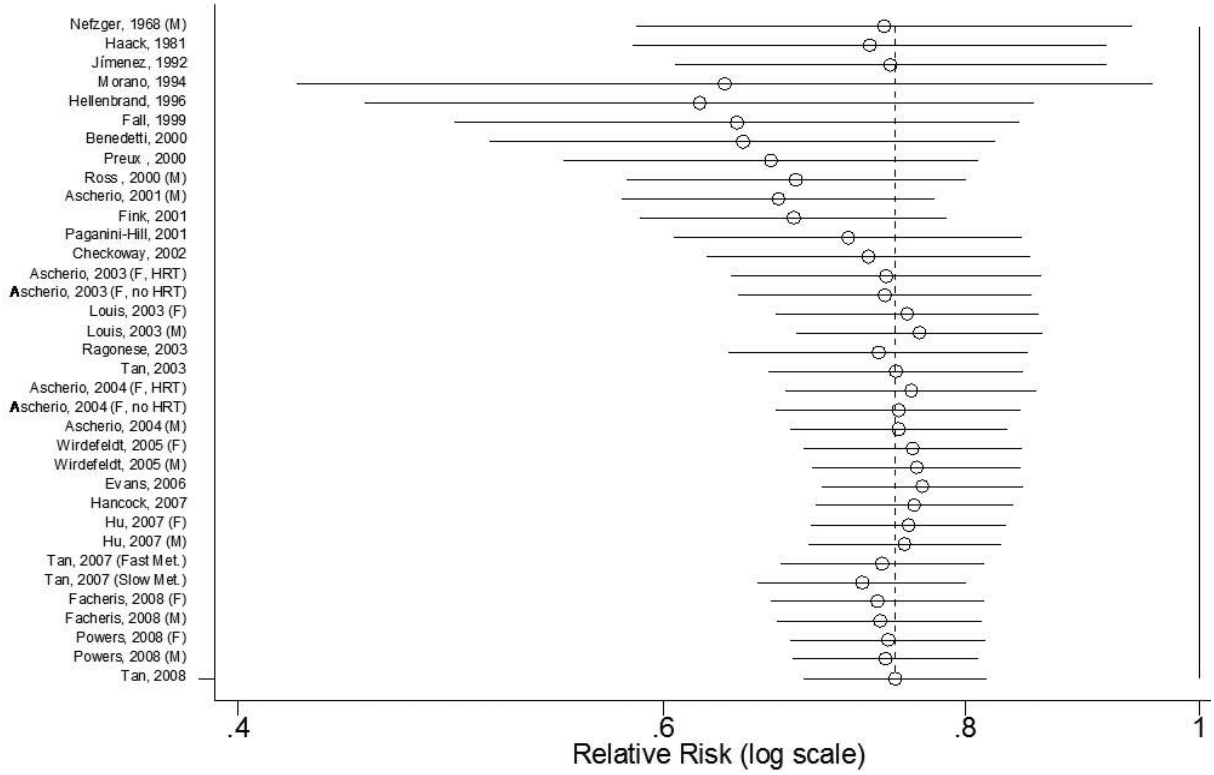

Fig. 4. Cumulative meta-analysis for the association between caffeine and Parkinson's disease, including the most precise Relative Risk estimates from each individual study. Legend: M – Male; F – Female; Fast Met. – Fast metabolizers; Slow Met. – Slow metabolizers; HRT – Hormonal Replacement Therapy.

used in other studies conducted by Ascherio et al.) and for one Italian study [37] the caffeine contents of a cup was assumed to be 75 mg (under the assumption that espresso coffee was more frequently consumed in this setting).

In all analyses heterogeneity was quantified using the I^2 statistic [41]. Publication and publication-related biases were examined through visual inspection of the funnel plot (Fig. 6). The Begg adjusted rank correlation [42] and the Egger's regression asymmetry test [43] were used for further assessment of these biases through hypothesis testing. All analyses were conducted with STATA®, version 9.2.

RESULTS

Systematic review

The search yielded a total of 134 reports (Fig. 1). A total of 26 epidemiological studies met criteria for inclusion in the systematic review, including 7 cohort [22, 23,28,29,33,35,40,44], 2 nested case-control [20,36], 16 case-control [15,16,18,19,21,26,30–32,34,37–39, 45–47] and one cross-sectional study [48]. The main characteristics of the studies and the respective results on the relation between caffeine intake and cognitive impairment are summarized in Table 1 and Fig. 2.

The publication year ranged from 1968 to 2008. The studies were conducted mainly in the USA (13 out of 26 [15,16,19,21,22,26,29,32,33,36,47,48], one of which in an Asian population [28]); in Europe (two in Spain [30,31], two in Sweden [20,**?**], one in Finland [23], one in France [18], one in Germany [45], one in Italy [37], one in the United Kingdom [38]); and in China [39,40,46].

Among the case-control studies, information on caffeine intake obtained from proxies or exclusion of cognitively impaired subjects was referred to in 4 [21,32, 34,46] and 3 reports [19,38,45], respectively. The study by Louis and colleagues [48] used both these strategies to minimize information bias. An accurate definition of the study base is not always possible with the information provided by the authors, but at least 5 were hospital based [15,30,31,37,38]. In cohort designs, the

Table 1

Main characteristics of the studies included in the systematic review

First author Country Publication year	Type of study Sample characteristics Follow-up (Cohort studies)	Outcome assessment Definition of Parkinson Disease/Parkinsonism	Evaluation of exposure Timing of exposure Validation of the method Items evaluated about caffeine exposure	Control of confounding
COHORT STUDIES				
Ross **USA** **2000 [28, 44]**	Cohort Study Japanese-American men (Honolulu-Asia Aging Study) Age: 45-68 y M/F: 8,006 (all M) Follow-up: Duration: 27 y (median); Completeness: NS	Review of hospital records, local neurologists records and death certificates (previous to 1991) After 1991, 3-step process: 1. Self declared diagnosis of PD (structured interview), PD medication 2. Evaluation by trained technician; recognition of PD clinical signs (tremor, gait disturbances, bradykinesia) 3. Referral to study neurologist – criteria for PD diagnosis (consensus from 2 neurologists): Parkinsonism Progressive disorder Any two of: marked response to levodopa, asymmetry at onset, or initial onset tremor Absence of other possible cause	24-hour recall methods and food frequency questionnaires 1 week before Validated Coffee, tea (green and black), other caffeinated beverages, and caffeine from other sources.	Age and Smoking
Ascherio **USA** **2001 [29]**	Cohort Study Male health professionals (Health Professionals' Follow-Up Study) Age: 40-75 47,351: all M Follow-up: Duration: 9.2 y (mean); Completeness: > 97%	Questionnaire (mail) Confirmation of diagnosis with the treating neurologist or by review of the medical records At least 2: Tremor, rigidity, bradykinesia Response to levodopa	SFFQ (mail) 1 year before Validated Coffee, tea, cola and chocolate	Age, smoking, alcohol, BMI, physical activity
Fink **USA** **2001 [35]**	Cohort Study Participants in the Original Framingham Study who attended the 12th, 17th or 22nd biennial examination Age: 69 y (mean) M/F: 2,382 / 3,746 Follow-up: Duration: 10 y (for each index examination); Completeness: NS	Physical examinations Tremor, rigidity, bradykinesia Absence of other possible cause	Structured questionnaire NS NS Coffee, tea	Age, gender, smoking

Table 1, continued

Ascherio **USA** **2003[33]**	Cohort Study Female registered nurses in 11 states (Nurses' Health Study) Age: 30-55 77,713 (1,039,434 person-years): all F Follow-up: Duration: 18 y (mean); Completeness: > 98%	Questionnaire (mail) Confirmation of diagnosis with the treating neurologist or by review of the medical records At least 2: Tremor, rigidity, bradykinesia Response to levodopa	SFFQ (mail) 1 year before Validated Coffee, tea, cola and chocolate	Age, smoking, alcohol, age at menopause, type of menopause, parity, use of oral contraceptives, and hormone use or duration of use
Ascherio **USA** **2004 [22]**	Cohort Study American Cancer Society volunteers (Cancer Prevention Study II) Age: ≥30 y (median: 57 for M; 56 for F) M/F: 301,164 / 238,058 Follow-up: Duration: 1989-1998; Completeness: 100%	PD as underlying or contributing cause of death National Death Index Idiopathic Parkinson's disease (ICD 9th revision)	Structured questionnaire NS NS Coffee, tea and sodas	Age, smoking, alcohol
Hu **Finland** **2007 [23]**	Cohort Study 4 cross-sectional population surveys in 1982, 1987, 1992 and 1997 Age: 25-74 y M/F: 14,293 / 15,042 Follow-up: Duration: 12.9 y; Completeness: 74-88%	National Social Insurance Institution's Register data Consultant (usually specialist in neurology) Medical history, clinical examination (tremor, bradykinesia, stiffness, etc) and other relevant diagnostic methods	Self-administered questionnaire at home. NS NS Coffee and tea	Age, BMI, systolic blood pressure, total cholesterol, education, leisure-time physical activity, smoking, alcohol and tea consumption, and history of diabetes
Tan **Singapore** **2008 [40]**	Cohort Study Ethnic Chinese, belonging to the two major dialect groups, and residing in government-built housing estates (Singapore Chinese Health Study). Age: 45-74 y (mean: 57 y) M/F: 27,956 / 35,262 Follow-up: Duration: 1993-2005; Completeness: 90%	Follow-up interviews, nationwide hospital discharge database and two hospital-specific Parkinson's disease registries 88 % of the cases were evaluated by a movement disorder specialists/ neurologist. Diagnosis criteria were those from the Advisory Council of the US National Institute of Neurological Disorders and Stroke	SFFQ (in-person interview at home made by a trained interviewer) NS Validated Coffee, black and green tea and sodas	Age, year of interview, gender, dialect, smoking and level of education
NESTED CASE-CONTROL STUDIES				
Paganini-Hill **USA** **2001 [36]**	Nested Case-Control Study within a prospective cohort study of 13,979 residents of Leisure World Laguna Hills (Leisure World Study, California). Cases and controls were selected from all residents that answered the health survey questionnaire sent by mail. Controls from the large cohort study were matched for age, gender, vital status and death date Cases /Controls: 395 (M/F: NS) / 2,320 Age: 75 y	Cases identified through review of hospital discharge diagnoses of cohort members for PD, review of death certificates and report of physician diagnosis of PD	Health survey questionnaire NS NS Coffee and tea	Age, gender, smoking, alcohol, blood pressure medication, vitamin A and C.

Table 1, continued

Wirdefeldt **Sweden** **2005 [20]**	Nested Case-Control Study Cases were 476 (M/F: 230/246) twins (mean age of 75 y) identified through the Swedish Inpatient Discharge Register and the Cause of Death Register. Two control groups: (1) randomly selected twins unrelated to the cases matched for birth year, gender and questionnaire source of the exposure data (external control subjects; n= 2,380); and (2) co-twins of the cases (co-twin control subjects; n=415 same-sex twin pairs). Mean Age: 75.3 years	Swedish Inpatient Discharge Register and the Cause of Death Register Idiopathic Parkinson's disease (ICD criteria)	Questionnaire sent to the twins in 1967 or in 1973 NS NS Coffee and tea	Matched for age, sex, genetic and familial environmental factors (twins) Smoking, alcohol and educational level.
CASE-CONTROL STUDIES				
Nefzger **USA** **1968 [15]**	Case-Control Study Cases were successive PD inpatients recruited from every neurologist (up to a maximum of 10 patients) in Veteran's hospitals throughout the country. Controls were the first patient registered after the PD case without psychiatric or extrapyramidal disease (matched for age) Cases/Controls: 198 (all M) / 198 Age: NS (>50% had ≥65 y)	Neurological examination Clinical diagnosis (criteria NS)	In-person interview NS NS Coffee	Matched for age
Haack **USA** **1981 [32]**	Case-Control Study Cases were recruited from medical records of PD cases seen by a neurologist in central Kentucky Controls were identified trough door-to-door in neighbourhood (matched for age, gender and race). Cases/Controls: 237 (M/F: 127/110) / 474 Age: 65 y (range, 25-89)	Neurological examination At least 2: bradykinesia, resting tremor, rigidity.	In-person interview (proxy if physically unable to answer questions) NS NS Coffee and tea	Matched for age, gender and race
Jiménez **Spain** **1992 [31]**	Case-Control Study Cases were unselected PD patients recruited from an outpatient movement disorder clinic (Madrid) Controls were patients presenting in the emergency room at the same hospital complaining of minor non-neurologic ailments (matched for age and gender). Cases/Controls: 128 (M/F: 68/60) / 256 Age: 65 y	Neurological examination Clinical diagnosis (criteria NS)	Personal interview assessing coffee drinking habits 5 years before NS Coffee	Matched for age and gender Smoking and alcohol
Morano **Spain** **1994 [30]**	Case-Control Study Cases were unselected outpatients making the first visit to one of two neurology clinics (Cáceres) Controls were patients presenting in the emergency room at the same hospital complaining of minor nonneurologic ailments (matched for age and gender). Cases/Controls: 74 (M/F: 33/41) / 148 Age: 68 y	Neurological examination Clinical diagnosis (criteria NS)	Questionnaire NS NS Coffee and tea	Matched for age and gender

Table 1, continued

Hellenbrand **German** **1996 [45]**	Case-Control Study Cases were all PD patients recruited from nine German neurologic clinics (aged ≤65 y – older patients were not recruited in order to minimize memory deficits). Controls were randomly selected from the same neighbourhood or region Cases/Controls: 342 (M/F: 224/118) / 342 Age: 56 y	Neurological examination UK Brain Bank criteria	SFFQ (in-person interview made by a trained interviewer) Before diagnosis of PD (cases) or 1 year before (controls) Validated Coffee and tea	Matched for age and gender Smoking, education and total energy intake.
Fall **Sweden** **1999 [34]**	Case-Control Study Cases were selected from prescription records and medical reports. Controls were randomly selected from population registry in the same area (Central Health Care District in Ostergotland County). Cases /Controls: 113 (M/F: NS) / 263 Age: 40-75 y (mean age: 63 y for cases and 57 for controls)	Neurological examination At least 1: hypokinesia, tremor, rigidity. No earlier treatment with neuroleptic drugs. Response to levodopa Progressive course Absence of atypical features	SFFQ (mail - proxy information when patients seemed unable to answer properly) 15 years before NS Coffee and tea	Age, gender, smoking, alcohol, occupation/exposure, food factors
Benedetti **USA** **2000 [26]**	Case-Control Study Cases were recruited from records linkage system of the Rochester Epidemiology Project. Controls were randomly recruited from the community (matched for gender and age). Cases/Controls: 196 (M/F: 121/75) / 196 Age: 71 y (range, 41-97)	Neurological revision of medical records (ICD codes) and full neurological examination in 27% of the cases. At least 2: bradykinesia, resting tremor, rigidity, postural instability Absence of other possible cause or atypical features Response to levodopa	Neurological revision of medical records NS Validated by telephone interview to a subsample of participants (direct and proxy interview) Coffee	Matched for age and gender Smoking, Alcohol
Preux **France** **2000 [18]**	Case-Control Study Cases were PD inpatients and outpatients of the Limoges University Hospital. Controls were inpatients and outpatients from other hospital departments (matched for age and gender). Cases and controls had to live in the region of Limousin for at least 20 years. Cases /Controls: 140 (M/F: 74/66) / 280 Age: 71 y	Neurological examination UK Brain Bank criteria	Standard questionnaire (physician personal interview) Lifetime NS Coffee and tea	Matched for age and gender Age, smoking, PD familial history, urban area, toxic products
Checkoway † **USA** **2002 [19, 61]**	Case-Control Study Cases selected from diagnosis logs at neurology and general clinics and from pharmacy database (Washington); MMSE to establish cognitive performance. Controls were from health cooperative enrolees (matched for gender, age, geographic location and year of enrolment) Cases/Controls: 210 (M/F: 131/79) / 347 Age: 71 y (range, 37-88)	Neurological examination or neurological panel review of charts At least 2: bradykinesia, resting tremor, rigidity, postural instability Absence of other possible cause or atypical features	Structured in-person questionnaire by a nurse practitioner at subjects home During most of adult life NS Coffee, tea, cocoa, cola drinks and chocolate	Age, gender, ethnicity and education.

Table 1, continued

Ragonese **Italy** **2003 [37]**	Case-Control Study Cases were consecutive outpatients at neurological clinics. Controls randomly selected from population records of the municipality (matched for gender, age and place of residence) Cases/Controls: 150 (M/F: 68/82) / 150 Age: 60 y (range, 31-81)	Neurological examination At least 2: bradykinesia, resting tremor, rigidity, postural instability Unilateral onset or asymmetry Response to levodopa Progressive course	Structured questionnaire Years of coffee consumption (0; 1-40; >40) NS Coffee	Education, smoking and alcohol
Tan **Singapore** **2003 [46]**	Case-Control Study Cases randomly selected from movement disorders database. Controls were participants in community health screening programme (matched for gender, age and race) Cases/Controls: 200 (M/F: 115/85) / 200 Age: 65 y (range, 43-88)	Neurological examination UK Brain Bank criteria	Structured questionnaire (interview) NS Validated (information from caregivers and family members) Coffee and tea	Matched for age, gender and race Tea, alcohol, smoking , head injury, stroke, hypertension, presence of heart conditions, toxin exposure and farm dwelling
Evans **UK** **2006 [38]**	Case-Control Study Cases were consecutive outpatients of Caucasian descent fulfilling Queen square brain bank criteria; MMSE to establish cognitive performance. Controls were friends of participants, outpatients without PD and randomly recruited from a volunteer panel (matched for age and gender) Cases/Controls: 106 (M/F: 65/41) / 106 Age: 65 y (range, 38-81)	Neurological examination Queen Square Brain Bank criteria	SFFQ (mail) 1 month before Validated Coffee, tea, chocolate milk, caffeinated soft drinks and chocolate	Matched for age and gender Sensation seeking score
Hancock **2007** **USA [16]**	Family-based Case-Control Study Cases recruited through physician- and self-referrals to an academic medical center clinic (Miami). Controls were siblings, spouses, parents of subjects, other branches of family. Cases/Controls: 356 (M/F: 235/121) / 317 Age: 66 y (mean, PD cases)	Neurological examination At least 2: bradykinesia, resting tremor, rigidity. Absence of atypical features.	Structured questionnaire (telephone) At reference age, 10 and 20 years before the reference age NS Coffee, tea and soft drinks	Age, gender, smoking and NSAIDs
Tan **Singapore** **2007 [39]**	Case-Control Study Cases were consecutive patients diagnosed with PD by a neurologist. Controls were volunteers from similar geographical regions (matched for age, gender and race). Cases/Controls: 418 (M/F: 243/175) / 468 Age: 70 y (mean, PD cases)	Neurological examination UK Brain Bank criteria	Standard questionnaire with a semiquantitative food frequency section NS Validated Coffee and tea	Age, gender and smoking

Table 1, continued

	Family-based Case-Control Study		Structured questionnaire (telephone - self or proxy for deceased or incapacitated subjects)	
Facheris	Cases were 604 (M/F: 336/238) patients (mean age of 65 y, range 32 to 92) referred sequentially to the department of Neurology of the	Neurological examination		
2008	Mayo Clinic (Rochester).		From birth to the age at onset	Age, gender, smoking and education
USA [21]	Two control groups: (1) siblings (n=446); and (2) unrelated controls (n=158) from the same geographic region matched for age, sex and ethnicity, selected randomly from Medicare and Medicaid services (if older than 65 y) or using random digit dialling (if younger than 65 y).	Detailed protocol (not specified)	Validated	
			Coffee, tea and caffeinated sodas	
	Case-Control Study		Standardized, self-administered questionnaire.	
Powers	Cases recruited sequentially through movement disorder clinics of NeuroGenetics	Neurological examination	Lifetime	
USA	Research Consortium (New York, Oregon, Washington and Georgia).			Age, gender, ethnicity, smoking, NSAIDs and state
2008 [47]	Controls were spouses and blood relatives of patients, and community volunteers.	UK Brain Bank criteria	NS	
	Cases/Controls: 1,186 (M/F: 790/396) / 928 Age: 69 y (range, 25-97)		Coffee	
CROSS-SECTIONAL STUDIES				
			Food frequency questionnaire	
Louis	Cross-sectional evaluation of coffee, smoke and parkinsonism	Neurologic and neuropsychological examinations		
USA	Participants in the Washington Heights–Inwood Columbia Aging Project cohort (random selection from healthy Medicare beneficiaries)		1 year before	Age, gender, ethnicity, smoking, years of education and dementia
2003 [48]	Mean age: 77 y M/F: 655 / 1,471	At least 2: bradykinesia, resting tremor, rigidity, postural instability.	Validated	
			Coffee	

BMI - Body Mass Index; ICD – International Classification of Diseases; NS – Not specified; NSAIDs - nonsteroidal antiinflammatory drugs; PD – Parkinson Disease; SFFQ - Semiquantitative Food-Frequency Questionnaire; UPDRS – Unified Parkinson's Disease Rating Scale

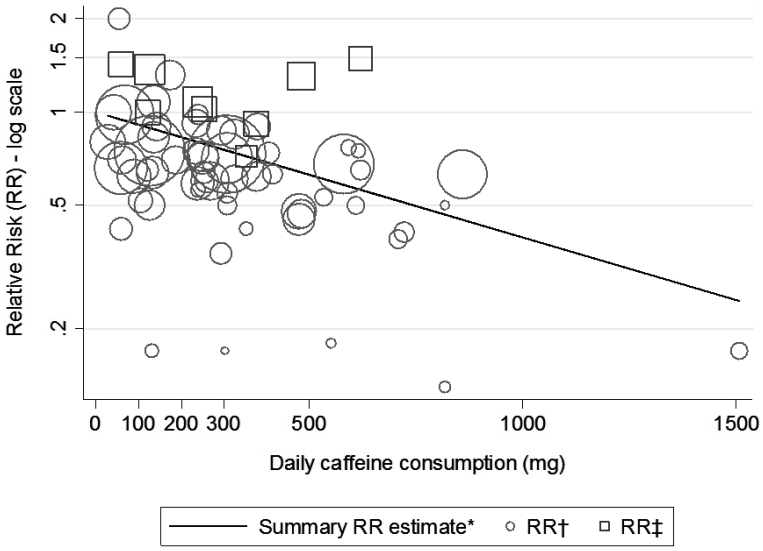

Fig. 5. Dose-response relation for the association between caffeine intake and the risk of Parkinson's disease. Legend: * Summary RR estimated by weighted least squares regression; † RRs for the comparison of each category of exposure with the reference category, obtained from each individual study; ‡ RRs for the comparison of each category of exposure with the reference category, obtained from the studies providing stratum-specific estimates for women under Hormonal Replacement Therapy [29,33].

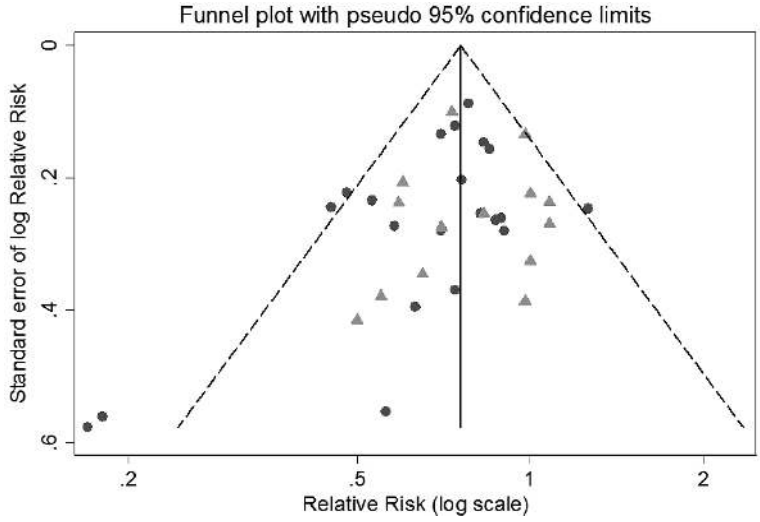

Fig. 6. Meta-analysis funnel plot, including the most precise Relative Risk estimates from each individual study. Legend: Circles – case-control/cross-sectional studies; Triangles – cohort/nested case-control studies.

estimated mean age of the participants at the time of baseline evaluation ranged from 42 to 77 years [33].

Different sources of caffeine were accounted for in the reports reviewed, and the results used for meta-analysis refer to coffee consumption in most studies ($n = 15$), to coffee and tea consumption in 5 studies, and 6 studies extended exposure assessment to all caffeinated beverages or caffeinated beverages and products containing chocolate. Seventeen out of 25 studies provided RR estimates for different categories of exposure, with an estimated daily exposure to caffeine ranging from 27.4 mg to 1507 mg, and the reference categories including different proportions of non-caffeine consumers and consumers of different amounts of caffeine. From one study we used the RR estimate for the variation in the consumption of one cup of coffee per day. The remaining studies only compared drinkers with non-drinkers.

The clinical diagnosis of PD, based on a set of predefined clinical criteria, was the outcome in most studies. Information obtained from medical records and national medication or inpatient databases were occasionally considered as a complementary source in 6 studies [19, 20,28,29,36,40], as well as from death certificates in 4 studies [20,28,33,36]. In two studies [16,40] some patients had PD defined by self report and not confirmed by a clinical diagnosis, death certificates or medical records. One study [22] assessed PD mortality as the sole outcome.

Regarding potential confounding factors, smoking was considered taken into account in 7 studies [15,16, 19,20,31,32,38]. Exposure to heavy metals and use of pesticides or herbicides was accounted for by 2 authors [18,46]. Age and gender were controlled for in all studies except that by Ragonese et al. [37], either by stratified analysis, matching or multiple regression.

Meta-analyses

The summary RR for the association between caffeine intake and PD was 0.75 (95%CI: 0.68–0.82), with low to moderate heterogeneity ($I^2 = 28.8\%$). The summary RR estimates were homogeneous ($I^2 = 8.1\%$) and slightly higher among the cohort/nested case-control studies, and the I^2 was 37.9% among the case-control studies (Fig. 3). The negative association was weaker when only women were considered for analysis (summary RR = 0.86, 95%CI: 0.73–1.02, 9 estimates from 7 studies, $I^2 = 12.9\%$) than when only men were considered for analysis (summary RR = 0.72, 95%CI: 0.65–0.81, 9 estimates from 9 studies, $I^2 = 0.0\%$) or both genders were considered (summary RR = 0.68, 95%CI: 0.57–0.81, 17 estimates from 16 studies, $I^2 = 50.3\%$).

The search date of the previous most recent systematic review on the risk of PD and caffeine exposure was 2001 [17]. The results of the cumulative meta-analysis (Fig. 4) show that since year 2001 the number of studies on this topic nearly doubled, corresponding to 14 new published studies (5 cohort/nested case-control and 9 case-control/cross-sectional studies). The results of these new studies allowed us to calculate a total of 23 RR estimates that were included in the present meta-analysis and confirmed the observation of a consistent and robust association between caffeine intake and PD. The summary RR was 0.72 (95%CI: 0.61–0.84) at the end of 2001 and is currently 0.75 (95%CI: 0.68-0.82), with no meaningful variation in heterogeneity (I^2: 26.6% in 2001 vs. 32.6% in 2008).

A linear relation was observed between levels of exposure to caffeine and the RR estimates (Fig. 5), corresponding to a summary RR of 0.76 (95%CI: 0.72–0.80) per 300 mg increase in caffeine intake, with moderate heterogeneity ($I^2 = 35.1\%$). Excluding the estimates corresponding to women under HRT from the studies by Ascherio et al. [22,33], the heterogeneity decreased ($I^2 = 27.6\%$).

Publication bias

The visual inspection of the funnel plot (Fig. 6) suggests that case-control/cross-sectional low precision studies yielding a positive association between caffeine intake and PD may be underrepresented in our meta-analysis, which is confirmed by the Egger's regression asymmetry test ($p = 0.053$) and the Begg adjusted rank correlation test ($p = 0.037$). On the other hand, for cohort/nested case-control studies, the funnel plot is symmetric and there is no evidence of statistically significant publication bias (Egger's regression asymmetry test: $p = 0.821$; Begg adjusted rank correlation test: $p = 0.412$).

DISCUSSION

The present meta-analysis shows a 25% reduction in risk of PD among caffeine consumers. The results also indicate a linear dose-response relation, with higher intakes of caffeine being associated with a lower risk of PD.

From a biological point of view, caffeine (1,3,7-trimethylxanthine) and its major metabolite, paraxanthine (1,7-dimethylxanthine), are antagonists of the adenosine A2A receptors. The expression of these receptors in the brain is particularly prominent in the striatum, which is the target of the dopaminergic neurons that degenerate in PD. Similar to other more specific A2A antagonists, caffeine attenuates neurotoxicity in experimental animal models of PD [49,50]. A recent study by Nakaso and collaborators provided further evidence for a possible neuroprotective effect of caffeine, showing that caffeine activates specific neuroprotection signaling pathways and prevents apoptotic cell death in a PD model using human dopaminergic neuroblastoma cells [51]. Therefore, there is a plausible rational biological mechanism based on the pharmacological actions of caffeine for the inverse association between coffee drinking and PD found in several epidemiological studies.

The primary candidate component that is believed to be responsible for the neuroprotective effect of coffee is caffeine. In fact, a negative association has also been reported for other non-coffee sources of caffeine, such as tea [46], but not for decaffeinated coffee [28]. However, coffee is a complex chemical mixture reported to contain more than a thousand different chemicals, including carbohydrates, lipids, nitrogenous compounds, vitamins, minerals, alkaloids, and phenolic compounds [52]. Thus, the possibility exists that other components of coffee or tea may also play a role. However, our systematic review was designed to test the effect of caffeine on the risk of PD under assumption that coffee is the main contributor to caffeine intake, and the specific effect of other caffeine containing beverages, such as tea, was not evaluated.

The negative association between caffeine intake and PD was consistent throughout different methodological approaches. Unlike those observed for cohort designs, the results from case-control/cross-sectional studies were somewhat heterogeneous, but consistently pointed to a protective effect, despite the observation that the strength of the association differed substantially across studies. Publication bias seems to have occurred for case-control/cross-sectional, but not for cohort/nested case-control studies, which may contribute to explain the stronger negative association observed among the former. Moreover, the homogeneity across results of cohort designs probably reflects a lower potential for bias with this methodological approach. Control selection is more likely to be biased in hospital-based case-control studies. Patients with PD may have an associated cognitive impairment [53], especially among older individuals, and this makes information bias more likely when exposure assessment is retrospective and exposure information is not collected from proxies. Also, patients with motor disability, such as in PD, may be less likely to drink coffee and this can only be accounted for with prospective designs or assessing exposure before the occurrence of the disease.

It has been suggested that PD patients may have a premorbid personality which may be responsible for particular addictive personality characteristics [54–58]. In PD, the progressive degeneration of the striatum with low endogenous dopamine and serotonin levels may lead to a low sensation seeking behavior (cause-effect bias) [59]. PD patients may therefore be less prone to smoke and drink coffee and alcohol, all lifestyle confounders with a potential neuroprotective or symptomatic effect in PD. Evans and coworkers [38] addressed this issue and raised the possibility of an existing neurobiological link between low sensation-seeking trait, which may underlie the parkinsonian personality, and the hypothetical protective effect of coffee in Parkinson's disease.

Cohort designs are less prone to information bias, but also have potential limitations related to the enrollment of non-inception cohorts and resulting from incomplete follow-up. Another potential source of bias is the definition of PD cases because of the lack of information regarding PD diagnoses in medical records and death certificates. Bias may also arise from exposure classification and quantification of coffee/caffeine consumption due to the different methods used in the studies, the low accuracy (recall bias) and reproducibility of the quantitative questionnaires, and the high variability of caffeine concentrations in coffee beverages.

It has been recognized that smokers have a lower risk of PD [17] and confounding by smoking habits is therefore an inherent problem when addressing the association between caffeine and PD. The majority of results available, however, were adjusted for smoking and other potential sources of bias, which makes confounding unlikely to be responsible for our conclusions.

The methodological options in our meta-analysis also need to be discussed. From studies presenting RRs for different categories of exposure we selected the most precise estimates to compute the summary RR for caffeine consumers vs. non-consumers, which allowed us to include all the available studies in the analysis. The precision of the individual RR estimates is not dependent on the direction of the association, and with this criterion the selection of the exposures corresponding to the largest number of participants is the most likely. However, if the categories of exposure in each individual study are defined to include a similar number of participants per group, this criterion leads to the selection of the estimates reflecting the weaker associations. This contributed to a slight underestimation of the summary RR, as well as an overestimation of homogeneity, especially for the cohort studies among which the definition of exposure categories with a similar number of participants was more frequent. The precision of the summary estimates, however, is underestimated by considering only part of the overall sample from each study in the meta-analysis.

For trend estimation we conducted a weighted linear regression adjusted through the origin, which implies the assumption of independence between all categories of exposure, an assumption that within each study is not met because all risk estimates depend on a common

referent group, ultimately leading to an underestimation of the slope variance. This contributes to spurious precision of our estimates but allows the computation of point estimates less prone to bias as it allows inclusion of most studies providing information for different categories of exposure. The use of a method that allows the correction for the lack of independence across RR estimates for different exposures would lead to the exclusion of some of the studies, as it requires more information than is provided by many studies [60].

A meta-analysis conducted by Hernán et al., published in 2002, concluded that smoking habits and coffee intake were independently associated with a lower risk of Parkinson's disease [17]. Despite the different options for meta-analysis, our review included nearly twice more individual studies and reaches robust conclusions that confirm the negative association between caffeine and PD. Also, the present meta-analysis adds to the previous one by confirming a linear dose-response relation, as previously suggested by Hernán and colleagues. Recent studies aiming to evaluate interactions with hormonal replacement therapy in women or hepatic caffeine metabolization were included [22,33,39], contributing to a broader view of the problem.

Ascherio and collaborators suggested gender differences in the relation of caffeine intake and the risk of PD: in men, a strong inverse association was found, whereas in women a U-shaped relationship was observed, with the lowest risk occurring at moderate intakes [29]. These authors further investigated this difference in two different cohorts and found an interaction between the use of postmenopausal hormones and caffeine intake in the risk of PD, with an increased risk among women on hormonal replacement therapy with a high caffeine intake [22,33]. The use of postmenopausal estrogens seems to modify the effects of caffeine on the risk of PD, although the reasons for this interaction are not yet clear.

The individual variability in the metabolism of coffee compounds related to genetic polymorphisms was also recently addressed [39]. The main endogenous system responsible for caffeine metabolism in humans is the cytochrome P450 1A2 (CYP 1A2). The study conducted by Tan and coworkers stratified the results for CYP 1A2 genetic polymorphism and demonstrated a similar dose-dependent PD protective effect of caffeine in individuals with fast and slow metabolizing status [39].

In conclusion, our data confirm an inverse association between caffeine intake and the risk of PD, with a dose-response relation, and more consistency in cohort studies and among men, which cannot be fully explained by bias or uncontrolled confounding. The understanding of the mechanisms for the protective effect of caffeine exposure warrants further investigation in PD.

DISCLOSURE STATEMENTS

Authors' disclosures available online (http://www.j-alz.com/disclosures/view.php?id=266).

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