A Meta-analysis of Coffee Drinking, Cigarette Smoking, and the Risk of Parkinson's Disease

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We conducted a systematic review to summarize the epidemiological evidence on the association between cigarette smoking, coffee drinking, and the risk of Parkinson's disease. Case–control and cohort studies that reported the relative risk of physician-confirmed Parkinson's disease by cigarette smoking or coffee drinking status were included. Study-specific log relative risks were weighted by the inverse of their variances to obtain a pooled relative risk and its 95% confidence interval (CI). Results for smoking were based on 44 case–control and 4 cohort studies, and for coffee 8 case–control and 5 cohort studies. Compared with never smokers, the relative risk of Parkinson's disease was 0.59 (95% CI, 0.54–0.63) for ever smokers, 0.80 (95% CI, 0.69–0.93) for past smokers, and 0.39 (95% CI, 0.32–0.47) for current smokers. The relative risk per 10 additional pack-years was 0.84 (95% CI, 0.81–0.88) in case–control studies and 0.78 (95% CI, 0.73–0.84) in cohort studies. Compared with non–coffee drinkers, relative risk of Parkinson's disease was 0.69 (95% CI, 0.59–0.80) for coffee drinkers. The relative risk per three additional cups of coffee per day was 0.75 (95% CI, 0.64–0.86) in case–control studies and 0.68 (95% CI, 0.46–1.00) in cohort studies. This meta-analysis shows that there is strong epidemiological evidence that smokers and coffee drinkers have a lower risk of Parkinson's disease. Further research is required on the biological mechanisms underlying this potentially protective effect.

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Coffee drinking and cigarette smoking have been associated with a lower risk of idiopathic Parkinson's disease (PD) in many epidemiological studies. Several mechanisms have been proposed to explain these inverse associations. Cigarette smoke may stimulate dopamine release and upregulate nicotinic receptors through nicotine, inhibit free radical damage to nigral cells through carbon monoxide, and protect against toxic neuronal damage by inhibition of monoamine oxidase B or competitive inhibition of neurotoxins.[1] Caffeine may counter the suppressive effect of adenosine on brain dopaminergic transmission by direct downregulation of adenosine A2a receptors and may inhibit the neurotoxicity induced by the chemical 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine.[2] The relevance of these mechanisms is, however, unclear.

Conversely, it has been suggested that the inverse association between cigarette smoking (and, more recently, coffee drinking) and PD is not causal, but entirely explained by various biases inherent to the design of the epidemiological studies that have been conducted. Potential biases include selective mortality of smokers among non-PD cases, lack of a proper recording of PD diagnoses among smokers, and confounding by unmeasured factors.[3,4] Some of these methodological concerns would be greatly attenuated if the inverse associations between coffee/smoking and PD risk were consistently found across different study designs and analytical strategies, or if their magnitude were large enough to make it unlikely that they can be fully accounted for by potential biases.

We conducted a systematic literature review of the association between coffee intake, cigarette smoking, and the risk of PD. This report summarizes the scientific evidence and quantifies the magnitude of those associations.

Materials and Methods

Systematic Search

We identified potentially eligible studies through a computerized Medline search including the period 1966 to January 1, 2002. The following search algorithm was applied to

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Medical Subjects Headings and free text words: (SMOK* OR TOBACCO OR CIGAR* OR COFFEE OR CAFFEINE) AND (PARKINSON OR PD) AND (CASE-CONTROL OR CASE-REFERENT OR RETROSPECTIVE OR COHORT* OR FOLLOW-UP OR INCIDENC* OR PROSPECTIVE OR EPIDEMIOLOG*). Similar search strategies were applied to the databases LILACS (Latin America and Caribbean) and Embase (Europe). We also examined conference proceedings, the references in the articles retrieved through the computerized search, and those in a previous review on smoking and PD.[1]

Eligibility Criteria and Data Collection

Studies eligible for the meta-analysis had to meet the following inclusion criteria: presentation of original data and a case–control or cohort design, PD as the outcome of interest, physician-confirmed diagnosis of PD, an odds ratio or relative risk (or enough information to compute it) reported to quantify the association between either cigarette smoking or coffee intake and PD diagnosis, and an attempt to ascertain exposure information that corresponded to a period before the PD diagnosis. Discrepancies in the selection of studies were discussed until a consensus was reached. If data from a study had appeared in more than one publication, the most recent one was used.

We developed a structured questionnaire to record the following data from the individual studies: design (cohort, case–control), number of participants (cases and controls, or cases and cohort size), type of controls (friends or relatives, patients with other diseases, community members or neighbors, combination of these groups), year of publication, adjustment factors, and association measures that compared PD risk among never smokers with that among ever, past, or current smokers, and similarly for non–coffee drinkers versus regular coffee drinkers. The information was extracted by two investigators. We took the definition of past, current, and never smoking used by the authors of the original report. When possible, we also obtained association measures per pack-year of smoking and per cup of coffee per day, either by estimating them from the reported results (see below) or by contacting the authors of the study.

Statistical Analysis

Study-specific log relative risks (cohort studies) or log odds ratios (case–control studies) were weighted by the inverse of their variances to obtain a pooled relative risk (RR) estimate and its 95% confidence interval (CI). Odds ratios were considered estimates of RRs. When fixed effects and random effects pooled estimates differed, we presented both. For pack-years of smoking and cups of coffee per day, we estimated the change in PD risk per unit of exposure (assuming linearity over the range of consumption reported in the studies) and then estimated a pooled regression parameter. We fit a logistic regression model for case–control studies, and a Poisson or Cox proportional hazards regression model for cohort studies.

We checked for heterogeneity using either the DerSimonian and Laird Q test statistic or, when the number of studies was low, its parametric bootstrap (1,000 replications) version.[5] To quantify heterogeneity, we calculated the proportion of the total variance due to between-study variance (Ri statistic). We evaluated the sources of heterogeneity by restricting the analysis to subgroups defined by study characteristics (study design, year of publication, adjustment factors). Because many studies were available to compare ever versus never smoking, we also evaluated sources of heterogeneity through metaregression of the log RRs on those study characteristics. We assessed potential publication bias using sensitivity analyses and funnel plots. All analyses were conducted with the software HEpiMA version 2.1.3,[6] and STATA version 6.0.

Results

Cigarette Smoking

The 44 case–control studies[7–50] (including 6,814 cases and 11,791 controls) and 4 cohort studies[4,51,52] that met the eligibility criteria were conducted in 20 countries between 1968 and 2001 (Table 1). Seven case–control studies used the UK PD Society Brain Bank Clinical Criteria[35,38,41,45,46] or the criteria of Calne[37,42] to make the diagnosis of PD. The remaining studies used the presence of cardinal signs and the effect of L-dopa, or relied on a neurologist's judgment. There was a diversity of control groups: friends or relatives,[10,13,15,23,43,46] patients with other diseases,[7,8,12,16,18–20,24–27,29,32,34,38,42,45] community members or neighbors,[9,11,21,22,28,30,35,36,39–41,44,47] or a combination of these groups.

Figure 1 summarizes the study-specific and pooled RRs of PD for ever smokers versus never smokers. Compared with never smokers, the pooled RR of PD was 0.59 (95% CI, 0.54–0.63) for ever smokers, 0.80 (95% CI, 0.69–0.93) for past smokers, and 0.39 (95% CI, 0.32–0.47) for current smokers (Table 2). The pooled RR of PD per 10 additional pack-years was 0.84 (95% CI, 0.81–0.88) in case–control studies,[12,30,35,39,40,43,44,46] and 0.78 (95% CI, 0.73–0.84) in cohort studies.[4,51,52] A fifth cohort study[53] also found an inverse association between smoking and risk of PD but could not be included in our pooled analysis because no association measures were reported.

The inverse association between smoking and PD risk was somewhat stronger in cohort studies than in case–control studies, especially for past versus never smokers (ie, RR 0.57 in cohort studies compared with 0.88 in case–control studies). The heterogeneity of the study-specific RRs was small to moderate within study design (Ri $<$ 0.40; see Table 2), and study characteristics, including type of controls, were very weakly associated with the magnitude of the RRs in the metaregression (data not shown).

To evaluate the possibility of publication bias in case–control studies, we recalculated our pooled estimates under the following extreme assumptions: (1) published studies listed in Table 1 are only half of the studies on smoking and PD risk ever conducted, (2) all

Table 1. Relative Risks and 95% Confidence Intervals of Parkinson's Disease According to Smoking Status

First Author, Year	RR (95% CI)			Adjustment	Cases/Controls or Cohort Size
	Ever Smokers	Past Smokers	Current Smokers		
Case–control studies					
Nefzger,[7] 1968	0.44 (0.27–0.74)	—	—	Not specified	198/198
Kessler,[8] 1971	0.64 (0.48–0.86)	—	—	Age, gender, race	468/468
Marttila,[9] 1980	0.74 (0.55–1.00)	1.40 (0.73–1.49)	0.38 (0.23–0.62)	Age, gender	443/443
Duvoisin,[10] 1981	1.00 (0.15–6.68)	5.50 (0.19–157.57)	0.28 (0.03–2.48)	Twin study	12/12
Haack,[11] 1981	0.48 (0.32–0.70)	—	—	Age, gender, race	237/474
Godwin-Austen,[12] 1982	0.56 (0.38–0.82)	0.71 (0.46–1.09)	0.40 (0.25–0.64)	Age, gender	383/383
Barbeau,[13] 1982	0.50 (0.20–1.23)	1.44 (0.40–5.21)	0.19 (0.07–0.53)	None	135/30
Ogawa,[14] 1984	0.45 (0.25–0.82)	0.53 (0.18–1.53)	0.43 (0.23–0.79)	Age, gender, personality	166/317
Bharucha,[15] 1986	0.30 (0.05–1.65)	—	—	Twin study	31/3
Rajput,[16] 1987	0.7 (0.4–1.2)	1.10 (0.60–2.03)	0.46 (0.23–0.92)	Age, gender, other not specified	118/236
Tanner,[17] 1987	0.68 (0.19–2.39)	—	—	Age	35/19
Ho,[18] 1989	0.6 (0.2–1.3)	—	—	Age, gender	35/105
Ngim,[19] 1989	0.61 (0.18–2.03)	—	—	Age, gender, race	54/95
Hofman,[20] 1989	0.60 (0.30–1.00)	—	0.70 (0.30–1.00)	Age, gender	86/172
Sasco,[21] 1990	0.97 (0.57–1.7)	—	—	Age, location, other not specified	96/384
Hertzman,[22] 1990	0.40 (0.19–0.86)	—	—	Age, gender, other not specified	57/122
Stern,[23] 1991	0.5 (0.3–0.9)	—	—	Age, gender, head injury	149/149
Wechsler,[24] 1991	0.57 (0.16–1.96)	—	—	Not specified	34/22
Zuber,[25] 1991	0.71 (0.42–1.22)	—	—	Age, gender, alcohol, coffee	150/114
Jiménez-Jiménez,[26] 1992	0.72 (0.45–1.13)	—	—	Age, gender, economic status	128/256
Butterfield,[27] 1993	0.32 (0.15–0.67)	—	—	Age, gender, race, education	63/68
Semchuk,[28] 1993	0.58 (0.33–1.20)	—	—	Age, gender, family history	130/260
Wang,[29] 1993	0.85 (0.54–1.36)	—	—	Age, gender, hospital	93/186
Mayeux,[30] 1994	0.8 (0.4–1.5)	0.9 (0.5–1.6)	0.2 (0.1–0.5)	Age, gender	285/416
Vieregge,[31] 1994	0.37 (0.18–0.73)	—	—	Age, gender	66/72
Martyn,[32] 1995	0.58 (0.39–0.88)	0.61 (0.40–0.94)	0.49 (0.26–0.91)	Age, gender	172/343
De Michele,[33] 1996	0.36 (0.17–0.73)	—	—	Age, gender	116/116
Liou,[34] 1997	0.42 (0.25–0.70)	—	—	Age, gender	120/240
Hellenbrand,[35] 1997	0.5 (0.3–0.7)	0.8 (0.5–1.2)	0.2 (0.1–0.4)	Age, gender, education	380/379
Tzourio,[36] 1997	1.1 (0.7–1.8)	1.4 (0.9–2.1)	0.7 (0.4–1.3)	Age, gender, dementia	193/579
McCann,[37] 1998	0.7 (0.4–1.1)	—	—	Age, gender, race, residence	224/310
Smargiassi,[38] 1998	0.41 (0.22–0.75)	—	—	Age, gender	86/86
Gorell,[39] 1999	0.58 (0.42–0.81)	—	—	Age, gender, race	144/464
Fall,[40] 1999	—	0.82 (0.44–1.51)	0.17 (0.06–0.43)	Age, gender	113/263
Kuopio,[41] 1999	0.91 (0.55–1.52)	—	0.5 (0.20–1.24)	Not specified	123/246
Werneck,[42] 1999	0.39 (0.16–0.95)	—	—	Age, gender	92/110
Taylor,[43] 1999	Shows pack-year results only			Age, gender, education, residency	140/147
Benedetti,[44] 2000	0.73 (0.41–1.32)	0.62 (0.38–1.01)	1.14 (0.41–3.15)	Age, gender, coffee, alcohol, education	196/196
Preux,[45] 2000	0.5 (0.3–0.8)	—	—	Age, other not specified	140/280
Vanacore,[46] 2000	0.50 (0.29–0.87)	—	—	Age, gender, center	140/134
Elbaz,[47] 2000	1.0 (0.6–1.7)	—	—	Age, gender, center	127/306
Paganini-Hill,[48] 2001[a]	—	0.92 (0.73–1.16)	0.42 (0.25–0.69)	Age, gender, vital status	395/2,320
Behari,[49] 2001	0.55 (0.36–0.84)	—	—	Age, other not specified	318/289
Herishanu,[50] 2001	0.36 (0.19–0.69)	—	—	Age, gender, pesticide exposure, job	93/93
Cohort studies					
Grandinetti,[51] 1994	0.39 (0.22–0.70)	0.50 (0.28–0.87)	0.25 (0.14–0.46)	Age, gender	58/8,004
Willems-Giesbergen,[52] 2001	0.54 (0.20–1.00)	—	—	Age, gender	53/6,969
Hernán (NHS),[4] 2001	0.59 (0.43–0.81)	0.7 (0.5–1.0)	0.4 (0.2–0.7)	Age, gender	153/121,700
Hernán (HPFS),[4] 2001	0.49 (0.35–0.69)	0.5 (0.4–0.7)	0.3 (0.1–0.8)	Age, gender	146/51,529

[a]Case–control study nested within a well-defined cohort with prospective data collection.

RR = relative risk; CI = confidence interval; NHS = Nurses' Health Study; HPFS = Health Professionals' Follow-up Study.

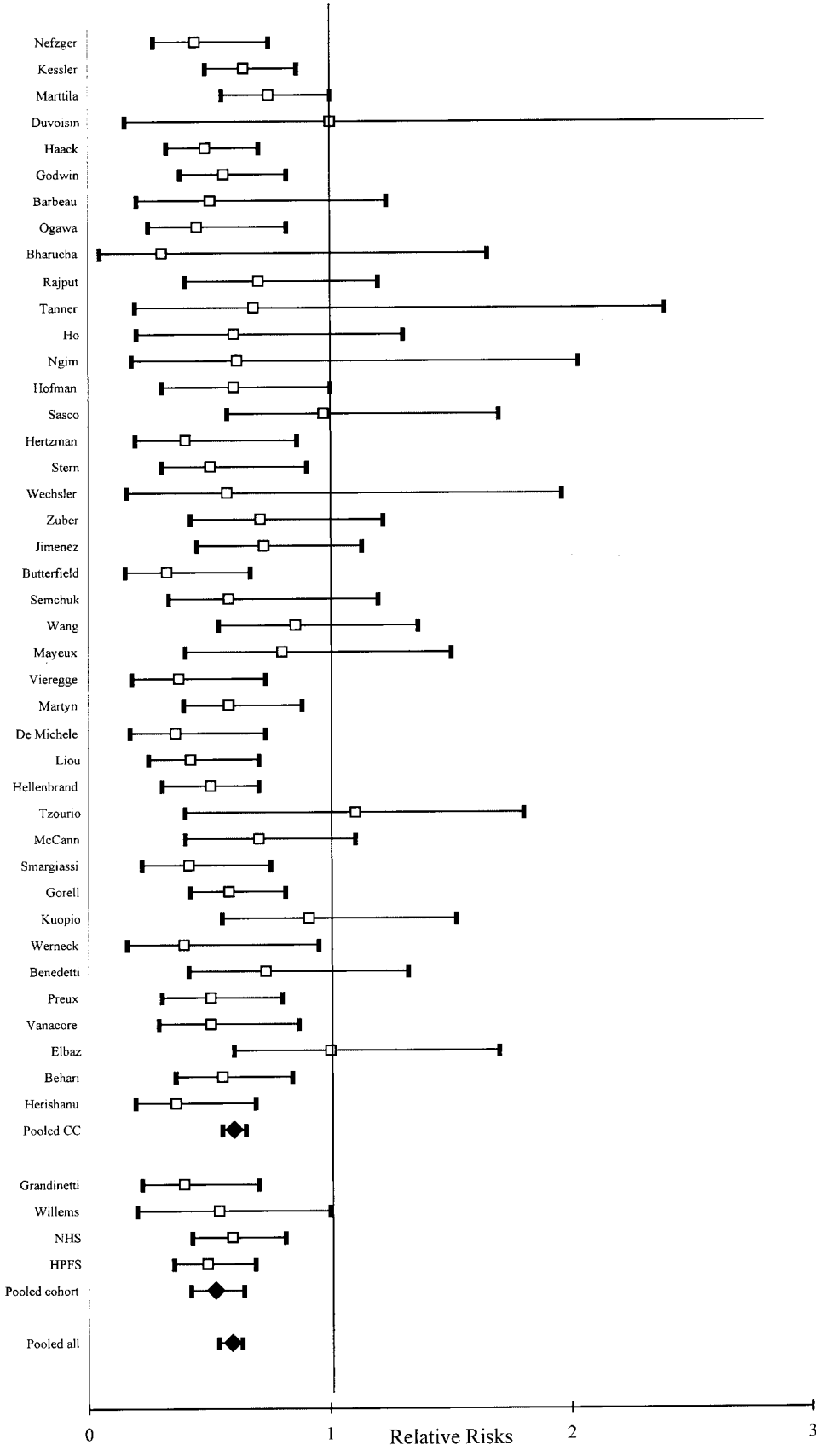


Fig 1. Study-specific and pooled relative risks from case–control and cohort studies on cigarette smoking and Parkinson's disease. CC = case–control study; NHS = Nurses' Health Study; HPFS = Health Professionals' Follow-up Study.

Table 2. Pooled Relative Risks and 95% Confidence Intervals of Parkinson's Disease according to Smoking Status

Smoking status	No. of Studies	RR[a] (95% CI) Fixed Effects	RR[a] (95% CI) Random Effects	Ri Statistic	Q Test (*p* Value)
Ever smokers					
All studies	45	0.59 (0.54–0.63)	0.58 (0.54–0.63)	0.07	0.35
Case–control studies	41	0.60 (0.55–0.65)	0.59 (0.55–0.65)	0.09	0.31
Cohort studies	4	0.52 (0.42–0.64)	0.52 (0.42–0.64)	<0.01	0.64
Past smokers					
All studies	16	0.80 (0.69–0.93)	0.80 (0.69–0.93)	0.40	0.06
Case–control studies	13	0.88 (0.78–1.00)	0.88 (0.75–1.02)	0.22	0.24
Cohort studies	3	0.57 (0.45–0.72)	0.57 (0.45–0.72)	0.04	0.35
Current smokers					
All studies	18	0.39 (0.32–0.47)	0.39 (0.32–0.47)	0.31	0.10
Case–control studies	15	0.41 (0.34–0.49)	0.41 (0.32–0.51)	0.37	0.08
Cohort studies	3	0.32 (0.22–0.47)	0.32 (0.22–0.47)	<0.01	0.53

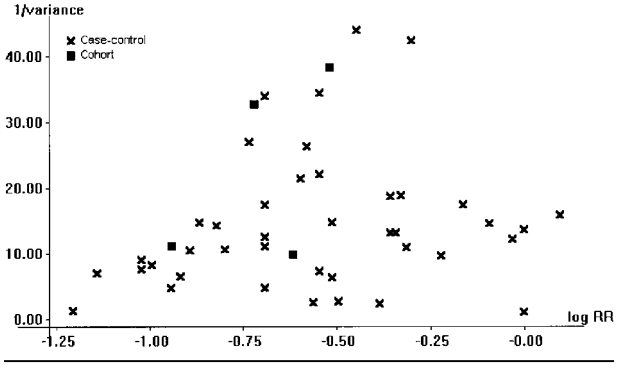
[a]Reference group is "never smokers."
RR = relative risk; CI = confidence interval.

studies of the unpublished half found null associations (ie, RR 1) between measures of smoking and PD, and (3) the unpublished studies included as many cases and controls as the published ones. Under these assumptions, the pooled RR of PD was 0.81 (95% CI, 0.76–0.87) for ever smokers, 0.95 (95% CI, 0.89–1.03) for past smokers, and 0.84 (95% CI, 0.78–0.91) for current smokers, compared with never smokers. Figure 2 displays the funnel plot of studies that compared the PD risk between ever and never smokers.

Coffee Intake

The 8 case–control studies[7,11,26,40,44,45,48,54] (including 1,440 cases and 4,016 controls) and 5 cohort studies[2,52,55,56] that met the eligibility criteria were conducted in four countries between 1968 and 2001 (Table 3). Figure 3 summarizes the study-specific and pooled RRs of PD for coffee drinkers versus non–coffee drinkers. Compared with non–coffee drinkers, the pooled RR of PD was 0.69 (95% CI, 0.59–0.80) for coffee drinkers (see Table 3). The pooled RR (95% CI) of PD per three additional cups of coffee per day was 0.75 (95% CI, 0.64–0.86) in case–control studies,[7,26,40,44] and 0.68 (95% CI, 0.46–1.00) in cohort studies.[2,52,55] A seventh case–control study also found a strong inverse association between coffee and PD when comparing the first and fifth quintiles of coffee consumption (odds ratio, 0.25; 95% CI, 0.14–0.44) but could not be included in our summary because the actual consumption of coffee was not reported.[57]

Fig 2. Funnel plot of case–control studies on cigarette smoking and Parkinson's disease. The log relative risk (RR) from each study is plotted on the horizontal axis, and an estimate of its precision (inverse of the variance) is plotted on the vertical axis.



The strength of the association was similar in case–control and cohort studies, and there was moderate heterogeneity of the RRs within study design (see Table 3). The results were virtually identical when we restricted the analyses to studies that presented RRs statistically adjusted for cigarette smoking. The RRs per additional cups of coffee per day from cohort studies showed marked heterogeneity (Ri = 0.84; P-value Q statistic = 0.004). Interestingly, the two cohort studies that included only men (ie, the Honolulu Heart Study[55] and the Health Professionals' Follow-up Study[2]) found a strong inverse linear relation between cups of coffee and risk of PD (pooled RR per three additional cups/day, 0.51; 95% CI, 0.31–0.83), whereas the cohort study that included only women (ie, the Nurses' Health Study[2]) found a virtually null linear relation (RR per three additional cups/day, 1.00; 95% CI, 0.74–1.34). In fact, the dose-response curve was U-shaped in this study.

To evaluate the possibility of publication bias in case–control studies, we recalculated our pooled estimates under the same extreme assumptions as for smoking: the RR of PD was 0.85 (95% CI, 0.75–0.97) for coffee drinkers compared with non–coffee drinkers. Figure 4 displays the funnel plot of

Table 3. Study-Specific and Pooled Relative Risks and 95% Confidence Intervals of Parkinson's Disease for Coffee Drinkers Compared with Non–Coffee Drinkers

First Author, Year	RR (95% CI)	Adjustment	Cases/Controls or Subjects Observed
Case–control studies			
Nefzger,[7] 1968	0.74 (0.58–0.93)	Not specified	198/198
Haack,[11] 1981	0.63 (0.29–1.36)	Age, gender, race	237/474
Jiménez-Jiménez,[26] 1992	0.82 (0.50–1.35)	smoking	128/256
Morano,[54] 1994	0.18 (0.06–0.54)	Age, gender	74/148
Fall,[40] 1999	0.47 (0.25–0.88)	smoking	112/242
Benedetti,[44] 2000	0.35 (0.16–0.78)	Age, gender, education, smoking, alcohol	178/175
Preux,[45] 2000	0.7 (0.4–1.2)	Age, other not specified	140/280
Paganini-Hill,[48] 2001[a]	0.85 (0.70–1.03)	Age, gender, smoking, alcohol, other	373/2,243
Cohort studies			
Ross,[55] 2000	0.45 (0.30–0.71)	Age, gender, smoking	102/8,004
Ascherio (NHS),[2] 2001	0.8 (0.6–1.0)	Age, gender, smoking, alcohol, BMI, physical activity	153/121,700
Ascherio (HPFS),[2] 2001	0.7 (0.5–0.9)	Age, gender, smoking, alcohol, BMI, physical activity	146/51,529
Fink,[56] 2001	0.89 (0.49–1.63)	Age, gender, smoking	58/6,048

Pooled results	All Studies	Case–Control Only	Cohort Only	Studies That Adjusted for Smoking
No. of studies	12	8	4	8
RR (95% CI), fixed effects	0.73 (0.66–0.81)	0.74 (0.65–0.84)	0.72 (0.62–0.84)	0.75 (0.67–0.84)
RR (95% CI), random effects	0.69 (0.59–0.80)	0.66 (0.52–0.83)	0.70 (0.56–0.88)	0.70 (0.59–0.84)
Ri statistic	0.46	0.56	0.49	0.50
Q Test (*p* Value)	0.05	0.05	0.14	0.07

[a]Case–control study nested within a well-defined cohort with prospective data collection.

RR = relative risk; CI = confidence interval; NHS = Nurses' Health Study; BMI = body mass index; HPFS = Health Professionals' Follow-up Study.

studies that compared the PD risk between coffee drinkers and non–coffee drinkers.

Discussion

Our results indicate that the risk of PD is 60% lower among current cigarette smokers than among never smokers, and 30% lower among coffee drinkers than among non–coffee drinkers. Each additional cup of coffee per day is associated with a risk reduction of 10%, although the magnitude of this reduction may differ by gender. PD risk also decreased as cumulative exposure to smoking (pack-years) increased.

Publication bias is a highly unlikely explanation for these results, because the inverse association between coffee drinking/cigarette smoking and PD remained strong even after extremely conservative assumptions regarding the number, size, and findings of studies potentially conducted and not included in our meta-analysis.

The high number of studies conducted, the magnitude of the associations found, and the consistency of the results across study designs and settings provide overwhelming epidemiological evidence that smokers have a lower risk of PD than nonsmokers. Traditionally, noncausal explanations proposed to explain this inverse association have been (1) that PD diagnoses are more frequently omitted in the death certificates and medical records of smokers (information bias), (2) that there is an increased mortality of younger smokers from causes other than PD (selection bias), and (3) that smoking and PD share common genetic or environmental causes (confounding).

As it has been argued previously,[4,58] explanations 1 and 2 are improbable because such information and selection biases would not have a substantial impact on the findings of properly conducted follow-up studies with prospective assessment of PD diagnoses, and thus these biases could hardly explain the strong inverse association found in all cohort studies. Furthermore, although the case–control design may be more prone to information and selection biases, the RRs for ever smoking and current smoking (vs never smoking) from case–control studies were only slightly weaker than those from cohort studies, which suggests that these biases are also relatively unimportant in the former. Conversely, the RR for past smokers was clearly stronger in cohort studies, possibly reflecting a greater misclassification of smoking history in case–control studies.

The presence of common causes (confounding) for both smoking and PD is another potential alternative explanation. For example, under the null hypothesis that current smoking and PD are not causally related,

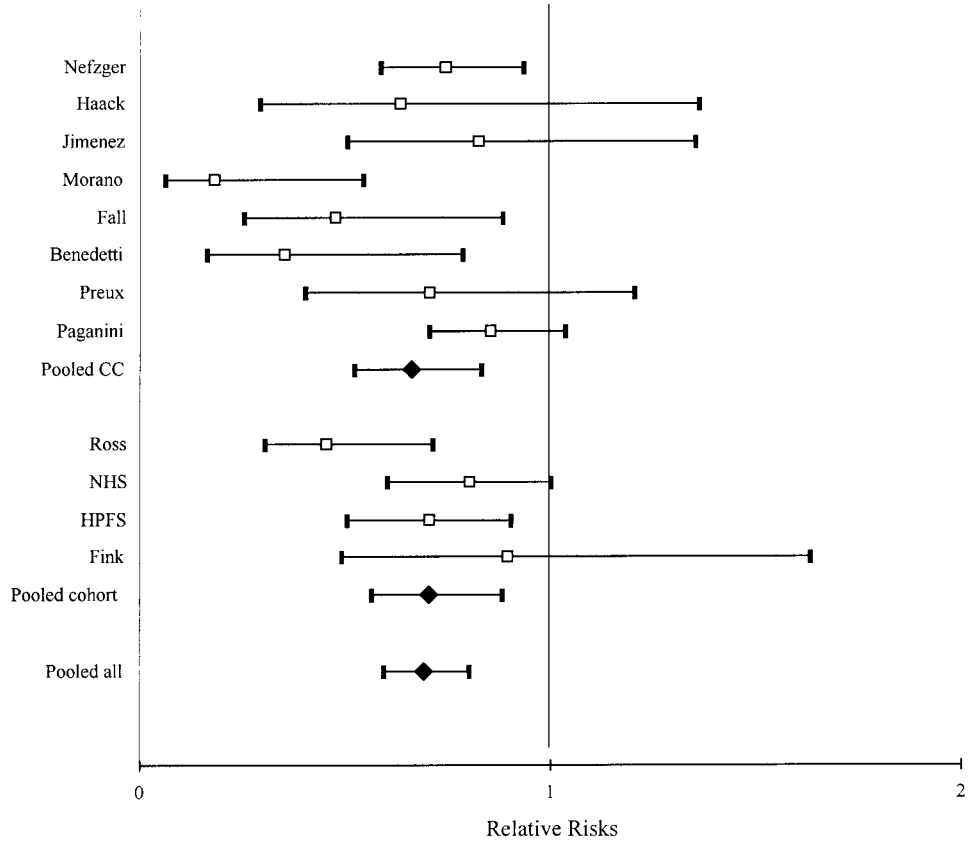
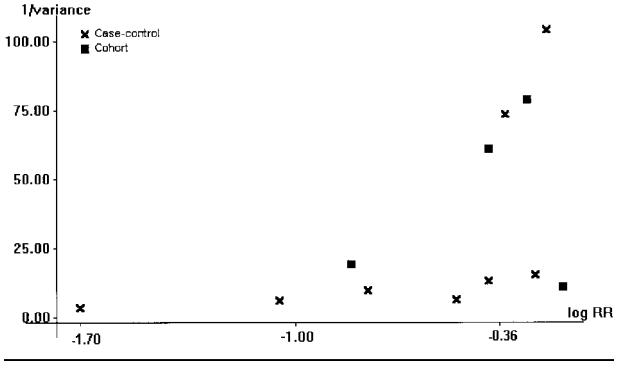


Fig 3. Study-specific and pooled relative risks from case–control and cohort studies on coffee drinking and Parkinson's disease. CC = case–control study; NHS = Nurses' Health Study; HPFS = Health Professionals' Follow-up Study.

the summary RR = 0.39 might be, theoretically, accounted for the presence of an unidentified genetic haplotype. However, even if the haplotype could make people harboring it five times more likely to develop PD and, simultaneously, five times more likely to abstain from cigarette smoking, the adjusted RR would still be 0.67 (assuming a third of people possess the haplotype).[59] The existence of an environmental agent so strongly associated with both smoking and PD, and yet unidentified, appears even more unlikely.

Fig 4. Funnel plot of case–control studies on cigarette smoking and Parkinson's disease. The log relative risk (RR) from each study is plotted on the horizontal axis, and an estimate of its precision (inverse of the variance) is plotted on the vertical axis.



A fourth alternative explanation is that patients with subclinical PD are less prone to initiate smoking or more likely to quit.[60] To disprove this "reverse causation" hypothesis is extraordinarily difficult. Some circumstantial evidence against this hypothesis has been provided by animal studies, which have shown that the brain of rats exposed to cigarette smoke have reduced concentrations of proneurotoxins supposedly involved in the cause of PD,[61] and that nicotine prevented parkinsonism in rodents.[62] If PD protects against establishing the habit of cigarette smoking then, because smoking behavior often starts in adolescence, subclinical PD ought to be already present in adolescence or childhood. This would imply a change in the currently widespread view of PD as an aging-related disease.

Therefore, the hypothesis that cigarette smoking protects against PD warrants further investigation. Several plausible biological mechanisms underlying this protective effect were reviewed by Morens and colleagues.[1] Although there appears to be little need for additional epidemiological studies on smoking and PD, research on these biological mechanisms is necessary.

The epidemiological evidence showing an inverse as-

sociation between coffee drinking and PD is very strong. Confounding and reverse causation (but not selection or information bias) can be alternative explanations to a truly protective effect of coffee drinking. Confounding is unlikely because eliminating the inverse association between coffee and PD (ie, RR = 1) would require adjusting for a dichotomous confounder (eg, a haplotype) associated with a fivefold increase in the risk of PD and with a fivefold decrease in the odds of becoming a coffee drinker (assuming a third of people have the haplotype). No such confounder, genetic or environmental, has been identified yet. Arguments against the reverse causation hypothesis are that it would imply a very early onset of PD, that animal experiments have found a neuroprotective effect of caffeine in mice exposed to compounds that cause parkinsonism,[63] that caffeine from noncoffee sources (eg, tea, cola beverages, chocolate) is also inversely associated with PD,[2,55] and that baseline intake was more strongly inversely associated with risk of PD than recent caffeine intake in cohort studies.[2,55]

Although the risk of PD decreases as caffeine intake increases among men (ie, in the Honolulu Heart Study and the Health Professionals' Health Study),[2,55] findings from the Nurses' Health Study, a cohort study including only women, suggest a U-shape dose-response curve among women. Additional analyses aimed at identifying potential effect modifiers (eg, sex hormones), new prospective data on coffee and PD among women (eg, from the Framingham Heart Study), and the pooling of data from case–control studies that included women will help clarify this issue.

In summary, both cigarette smoking and coffee drinking are inversely associated with the risk of PD. These results are consistent across study designs and geographical settings and may reflect a protective effect of smoking and coffee drinking on PD risk. From a public health standpoint, any benefits of smoking on PD would be overwhelmed by its effects on cancer, heart disease, respiratory disease, and overall mortality. Whether these inverse associations correspond to protective effects of components of cigarette smoke and caffeine, or whether they reflect changes in behavior that precede the motor manifestations of the disease, further research on the specific mechanisms involved in either case might lead to advances in the prevention and treatment of PD.

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