

Smoking and Parkinson's and Alzheimer's disease: review of the epidemiological studies

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Abstract

The relationship between smoking and neurological diseases has always been controversial. Even the expected association between smoking and increased risk for cerebrovascular disease has been debated for years. It was at the end of the 1980s that smoking became definitively accepted as a risk factor for ischemic stroke. More recently, two other neurological diseases have been studied in relation to smoking: Parkinson's disease (PD) and Alzheimer's disease (AD). Many epidemiological studies have found a highly significant negative association between cigarette smoking and these two neurodegenerative disorders. The risk of AD or PD in nonsmokers has generally been about twice that of smokers. That is, patients with AD or PD are $\approx 50\%$ less likely to have smoked cigarettes during their lifetime than are age- and gender-matched controls. Alternatively, cigarette smokers are $\approx 50\%$ less likely to have PD or AD than are age- and gender-matched nonsmokers. This statistically significant negative association has been interpreted as suggesting that cigarette smoking exerts an undefined, biologic, neuroprotective influence against the development of PD and AD. A review of all studies that either support or refute this hypothesis is presented separately for PD and AD. © 2000 Elsevier Science B.V. All rights reserved.

Keywords: Alzheimer's disease; Parkinson's disease; Smoking; Incidence; Prevalence; Mortality

1. Introduction

Smoking has been extensively studied in relation to different brain disorders, mainly vascular and degenerative diseases. The relationship between smoking and neurological diseases, however, has always been controversial. Even the expected association between smoking and increased risk for cerebrovascular disease has been debated for years. It was only at the end of the 1980s that smoking became definitively accepted as a risk factor for ischemic stroke [1]. More recently, two other neurological diseases have been studied in relation to smok-

ing: Parkinson's disease (PD), and Alzheimer's disease (AD). Many epidemiological studies have found a highly significant negative association between cigarette smoking and these two neurodegenerative disorders. The reported risk of AD or PD in nonsmokers is generally about twice that of smokers. That is, patients with AD or PD are $\approx 50\%$ less likely to have smoked cigarettes during their lifetime than have age- and gender-matched controls. Alternatively, cigarette smokers are $\approx 50\%$ less likely to have PD or AD than are age- and gender-matched nonsmokers. This statistically significant negative association has been interpreted as a protective effect of smoking against the development of PD and AD. The hypothesis is that cigarette smoking might exert a biologic, neuroprotective influence against neurodegeneration. A review of all studies that either support or refute this hypothesis is presented separately for PD and AD.

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2. Methodological considerations

When reviewing the literature concerning smoking and neurodegenerative disorders in the elderly, two main methodological aspects need to be taken into account.

First, most of the studies carried out on AD and PD, included prevalent cases, that is, all subjects affected by the disease in a defined area or hospital during the detection time. This means that the prevalent cases are selected towards those who have more chance to survive after they have developed the disease. When studying a risk factor that is also a prognostic factor for that disease (e.g. it affects the natural history such as mortality), the inclusion of prevalent cases in epidemiological studies may cause survival bias. This is the case for smoking that has been shown to affect survival among PD and AD subjects more than among controls. In Fig. 1, data from our longitudinal study on aging and dementia, the Kungsholmen Project, are reported [41]. Subjects with AD survived less than the controls and smoking affected their risk of death much more than

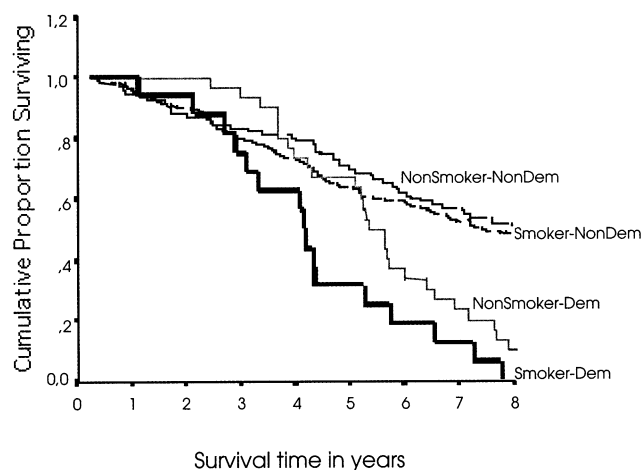


Fig. 1.

Table 1
Prospective studies concerning cigarette smoking and Parkinson's disease

References	Risk estimates (RR/SMR)
Dorn (1959) [9]	0.36*
Kahn (1966) [27]	0.23*
Hammond (1966) [20]	0.76†
Doll and Peto (1976) [8]	0.43†*
Hirayama (1985) [23]	0.57
Grandinetti et al. (1994) [16]	0.39*
Morens et al. (1996) [32]	0.40

* Males only.

† Indicates associations that were not statistically significant at the level of $P < 0.05$. All other associations were statistically significant ($P < 0.05$).

the risk of death in the controls. In the non-dementia group, smoking was not associated with greater mortality: age-, sex- and education-adjusted hazard ratio was 0.8, 95% CI = 0.5–1.2. In the dementia group, smoking was associated with a significantly higher mortality: age-, sex- and education-adjusted hazard ratio was 3.5, 95% CI = 1.4–8.8. The interaction effect between smoking and dementia proved significant ($P = 0.04$). Survival bias can be eliminated by using a prospective study with detection of incident cases.

Second, the entire group of smokers who survive until old age is likely to be a selected group of subjects due to the high mortality among smokers. The differential survival between smokers and nonsmokers may be the explanation of the negative association found between smoking and neurodegenerative disorders. Riggs (1996) [36], suggests that smokers not only die sooner than nonsmokers, but also die from different diseases. Thus, the differential survival leads to a gene pool of surviving smokers different from that of surviving nonsmokers. This hypothesis explains the neuroprotection of smoking as an artifact caused by 'life selection'. At present, no data are really available to test such hypothesis. However, the selection due to differential mortality in smokers, needs to be taken into account. This selection is not eliminated by using longitudinal study of the elderly.

3. Smoking and Parkinson's disease

More than 40 epidemiological studies have been published on this topic. The earliest reports of a negative association between smoking and PD were derived from mortality studies in 1959 [9]. Later, some studies, both case-control and longitudinal, were carried out, mostly confirming such negative association. An extensive and critical review was published in 1995 [33]. In Table 1 the risk estimates from prospective investigations are reported: all studies, including a 29-year follow-up from the Honolulu Heart Study [32], found a protective effect. In this study, both incidence and mortality rates of idiopathic PD were detected among smokers and nonsmokers. The incidence for PD in smokers was less than half that in nonsmokers and the lower incidence was present in all age strata. The adjusted relative risk was 0.4 (95% CI = 0.3–0.6). Subjects with and without PD showed similar increased mortality in smokers than in nonsmokers. Moreover, the authors underlined that the small differential mortality between smokers and nonsmokers in younger ages did not easily account for a large 'life selection' able to explain the negative association between smoking and PD found in old age. These last two observations provide strong evidence against the hypothesis that the association between smoking and reduced PD

Table 2

Dose–response relationship between Parkinson's disease and smoking and its cessation [15]

Smoking history	Adjusted OR (95% CI)
Never smoked	1 (reference)
Current light smokers	0.6 (0.2–1.5)
Current heavy smokers	0.1 (0.01–0.6)
Former heavy smokers – stopped > 20 years ago	0.9 (0.4–1.8)
Former heavy smokers – stopped 1–20 years ago	0.4 (0.2–0.7)

Table 3

Epidemiological studies concerning cigarette smoking and Alzheimer's disease

Findings	Number of case-control studies	Number of follow-up studies
Inconclusive results [2,5–7,12,13,18,22,24,25,28,31,35,39]	14	–
Smoking is a risk factor [3,26,38];[14,34]	3	2*
Smoking is a protective factor [4,10,19,37,40];[17,30]	5/2 studies/ metanalysis	–
No association [11,21,29]	–	3#

* One study concerned cognitive impairment [14].

Two studies concerned cognitive impairment [11,29].

Table 4

Finding from the Kungsholmen Project concerning the relation between smoking and Alzheimer's disease [41]^a

	Case-control study OR (95% CI)	Follow-up study RR (95% CI)
Crude	0.6 (0.4–1.1)	0.8 (0.4–1.7)
Adjusted for age, sex and education	0.6 (0.4–1.1)	1.1 (0.5–2.4)

^a OR, odds ratios were computed from logistic regression models. RR, relative risks were computed from Cox's regression models.

incidence is due to selective mortality in younger ages and/or among diseased subjects.

Finally, a recently published population-based case-control study from the Henry Ford Health System database [15] have strongly confirmed the negative association. In spite of the retrospective assessment of the smoking habits, this study has the strength of reporting a clear dose–response relationship between PD and smoking and its cessation (Table 2).

4. Smoking and Alzheimer's disease

The relationship between smoking and AD has not been explored to the same extent as between smoking and PD. Moreover, the results are largely inconsistent. A summary of the studies is reported in Table 3. Most of the studies have reported inconclusive results [2,5–7,12,13,18,22,24,25,28,31,35,39]. Recently, results from some case-control studies have suggested an inverse association [4,10,19,37,40], confirmed by two meta-analyses [17,30]. This inverse association was supported by the findings of a significant dose-dependent relation [17,40].

All these studies reporting a protective effect included prevalent cases and could have introduced a survival bias. We verified this hypothesis by using the data from the Kungsholmen Project. We found that smoking affected survival in persons with AD much more than in nondementia subjects (Fig. 1). Thus, it is likely that smokers who succumb to dementia might be eliminated early from the population, resulting in an underrepresentation of smokers with dementia in cross-sectional samples. Further, we estimated the risk of dementia in the same cohort initially by using a case-control study design including prevalent cases, then by estimating the relative risk with follow-up data (Table 4). The prospective study failed to confirm the protective effect of smoking on the occurrence of AD that we found in the case-control study [41]. This finding from the Kungsholmen Project is in agreement with a prospective study from Boston, MA [21] and with two other longitudinal surveys examining cognitive impairment [11,29].

Finally, from The Rotterdam Study, a positive association between smoking and the incidence of AD has been reported, limited to subjects without any apolipoprotein-E $\epsilon 4$ allele [34]. Only one other prospective study has shown a similar positive effect between smoking and cognitive impairment [14].

5. Conclusions

The following considerations have emerged: (1) The negative association of PD with smoking has been consistently found, whereas for AD such an association is controversial; (2) Many possible biases, foremost of all, survival bias, which may be responsible for the negative association have been taken into account in PD research and partially ruled out. This is not the case for AD studies; and (3) Some studies reported a positive association between AD and smoking, but the known relationship between smoking and cerebrovascular disease was only partially taken into account. In conclusion, there is evidence concerning a protective effect of smoking in PD, but not a clear effect in AD. Smoking seems to play a causative role in dementia and

cognitive impairment, possibly due to the known risk effect for vascular diseases.

References

- [1] Abbott RD, Rodriguez BL, Burchfiel CM, Curb JD. Physical activity in older middle-aged men and reduced risk of stroke: the Honolulu Heart Program. *Am J Epidemiol* 1994;139:881–93.
- [2] Amaducci LA, Fratiglioni L, Rocca WA, et al. Risk factors for clinically diagnosed Alzheimer's disease: A case-control study of an Italian population. *Neurology* 1986;36:922–31.
- [3] Barclay L, Kheifets S. Tobacco use in Alzheimer's disease. *Prog Clin Biol Res* 1989;317:189–94.
- [4] Brenner DE, Kukull WA, van Belle G, et al. Relationship between cigarette smoking and Alzheimer's disease in a population-based case-control study. *Neurology* 1993;43:293–300.
- [5] Broe GA, Henderson AS, Creasey H, et al. A case-control study of Alzheimer's disease in Australia. *Neurology* 1990;40:1698–707.
- [6] Chandra V, Philipose V, Bell PA, et al. Case-control study of late onset probable Alzheimer's disease. *Neurology* 1987;37:1295–300.
- [7] Dewey ME, Davidson IA, Copeland JRM. Risk factors for dementia: evidence from the Liverpool study of continuing health in the community. *Int J Geriatr Psychiatry* 1988;3:245–9.
- [8] Doll R, Peto R. Mortality in relation to smoking: 20 years' observations on male British doctors. *Br Med J* 1976;2:1525–36.
- [9] Dorn HF. Tobacco consumption and mortality from cancer and other diseases. *Publ Health Rep* 1959;74:581–93.
- [10] Ferini-Strambi L, Smirne S, Garancini P, et al. Clinical and epidemiological aspects of Alzheimer's disease with presenile onset: a case-control study. *Neuroepidemiology* 1990;9:39–49.
- [11] Ford AB, Mefrouche Z, Friedland RP, et al. Smoking and cognitive impairment: a population-based study. *J Am Geriatr Soc* 1996;44:905–9.
- [12] Forster DP, Newens AJ, Kay DWK, et al. Risk factors in clinically diagnosed presenile dementia of the Alzheimer type: a case-control study in northern England. *J Epidemiol Community Health* 1995;49:253–8.
- [13] French LR, Schuman LM, Mortimer JA, et al. A case-control study of dementia of the Alzheimer type. *Am J Epidemiol* 1985;121:414–21.
- [14] Galanis DJ, Petrovitch H, Launer LJ, Harris TB, Foley DJ, White LR. Smoking history in middle age and subsequent cognitive performance in elderly Japanese-American men. *Am J Epidemiol* 1997;145:507–15.
- [15] Gorell JM, Rybicki BA, Johnson CC, Peterson EL. Smoking and Parkinson's disease: A dose-response relationship. *Neurology* 1999;52:115–9.
- [16] Grandinetti A, Morens DM, Reed D, et al. Prospective study of cigarette smoking and the risk of developing idiopathic Parkinson's disease. *Am J Epidemiol* 1994;139:1129–38.
- [17] Graves AB, van Duijn CM, Chandra V, et al. Alcohol and tobacco consumption as risk factors for Alzheimer's disease: A collaborative re-analysis of case-control studies. *Int J Epidemiol* 1991;20(Suppl. 2):48–57.
- [18] Graves AB, White E, Koepsell T, et al. A case-control study of Alzheimer's disease. *Ann Neurol* 1990;28:766–74.
- [19] Grossberg GT, Nakra R, Woodward V, et al. Smoking as a risk factor for Alzheimer's disease. *J Am Geriatr Soc* 1989;37:819 [Letter].
- [20] Hammond EC. Smoking in relation to the death rates of one million men and women. In: Haenszel W, editor. *Epidemiologic Approaches to the Study of Cancer and Other Chronic Diseases*, vol. 19. National Cancer Institute Monograph, Bethesda, MD: US Department of Health, Education and Welfare, 1966:127–204.
- [21] Hebert LE, Scherr PA, Beckett LA, et al. Relation of smoking and alcohol consumption to incident Alzheimer's disease. *Am J Epidemiol* 1992;135:347–55.
- [22] Heyman A, Wilkinson WE, Stafford JA, et al. Alzheimer's disease: A study of epidemiological aspects. *Ann Neurol* 1984;15:335–41.
- [23] Hirayama Y. Epidemiological patterns of Parkinson's disease based on a cohort study. In: *Epidemiology of Intractable Diseases Research Committee*, editor. Tokyo: Japan Ministry of Health and Welfare, 1985:219–27 [in Japanese].
- [24] Hofman A, van Duijn CM. Alzheimer's disease, Parkinson's disease and smoking. *Neurobiol Aging* 1990;11:295 [Abstract].
- [25] Jones GMM, Reith M, Philpot MP, et al. Smoking and dementia of Alzheimer's type. *Neurol Neurosurg Psychiatry* 1987;50:1383 [letter].
- [26] Joya CJ, Pardo CA, Londono JL. Risk factors in clinically diagnosed Alzheimer's diseases: A case-control study in Colombia (South America). *Neurobiol Aging* 1990;11:296 [Abstract].
- [27] Kahn HA. The Dorn study of smoking and mortality among US veterans: report on eight and one-half years of observation. In: Haenszel W, editor. *Epidemiologic Approaches to the Study of Cancer and Other Chronic Diseases*, vol. 19. Bethesda, MD: National Cancer Institute, 28 Monograph, US Department of Health, Education and Welfare, 1966:1–25.
- [28] Kondo K, Yamashita I. A case-control study of Alzheimer's disease in Japan. In: Hasegawa K, Homma A, editors. *Association with Inactive Psychosocial Behaviors, Psychogeriatrics: Biomedical and Social Advances*. Amsterdam: Excerpta Medica, 1990:49–53.
- [29] Launer LJ, Feskens EJM, Kalmijn S, et al. Smoking, drinking, and thinking. The Zutphen Elderly Study. *Am J Epidemiol* 1996;143:219–27.
- [30] Lee PN. Smoking and Alzheimer's disease: A review of the epidemiological evidence. *Neuroepidemiology* 1994;13:131–44.
- [31] Li G, Shen YC, Li YT, et al. A case control study of Alzheimer's disease in China. *Neurology* 1992;42:1481–8.
- [32] Morens DM, Grandinetti A, Davis JW, Ross GW, White LR, Reed D. Evidence against the operation of selective mortality in explaining the association between cigarette smoking and reduced occurrence of idiopathic Parkinson disease. *Am J Epidemiol* 1996;144:400–4.
- [33] Morens DM, Grandinetti A, Reed D, White LR, Ross GW. Cigarette smoking and protection from Parkinson's disease: False association or etiologic clue? *Neurology* 1995;45:1041–51.
- [34] Ott A, Slioter AJC, Hofman A, et al. Smoking and risk of dementia and Alzheimer's disease in a population-based cohort study: the Rotterdam study. *Lancet* 1998;351:1840–3.
- [35] Prince M, Cullen M, Mann A. Risk factors for Alzheimer's disease and dementia: A case-control study based on the MRC elderly hypertension trial. *Neurology* 1994;44:97–104.
- [36] Riggs JE. The 'protective' influence of cigarette smoking on Alzheimer's and Parkinson's diseases. *Neuroepidemiology* 1996;14:353–8.
- [37] Salib E, Hillier V. A case-control study of smoking and Alzheimer's disease. *Int J Geriatr Psychiatry* 1997;12:295–300.
- [38] Shalat SL, Seltzer B, Pidcock C, et al. Risk factors for Alzheimer's disease: A case control study. *Neurology* 1987;37:1630–3.
- [39] Soininen H, Heinonen OP. Clinical and etiologic aspects of senile dementia. *Eur Neurol* 1982;21:401–10.
- [40] van Duijn CM, Hofman A. Relation between nicotine intake and Alzheimer's disease. *Br Med J* 1991;302:1491–4.
- [41] Wang HX, Fratiglioni L, Frisoni GB, Viitanen M, Winblad B. Smoking and the occurrence of Alzheimer's disease. *Am J Epidemiol* 1999;149:640–4.