Smoking, Alzheimer's disease, and confounding with genes

SIR—Plassman and colleagues (Feb 11, p 387) postulate that confounding with genes might explain the inverse association of smoking with Alzheimer's disease. According to this hypothesis, if individuals with a genetic predisposition to cigarette smoking are also predisposed to not develop Alzheimer's disease (AD), then the inverse association between cigarette smoking and AD is an artifact of genetic confounding. In support of this hypothesis, they investigated 32 monozygotic (MZ) and 33 dizygotic (DZ) elderly twin pairs who were discordant for AD. They say that "the inverse association of smoking and AD disappeared in this sample when genotype was fully controlled in MZ pairs".

First, as Plassman and colleagues note, the difference in the strength of the association between smoking and AD in MZ and DZ twin pairs was not statistically significant. Second, they do not report the percentage of smokers in the four patient populations (AD-MZ, normal-MZ, AD-DZ, normal-DZ), making interpretation of their data difficult. Third, the epidemiology of smoking and AD is controversial because of concerns that there might be diagnostic misclassification of smokers. For example, lesions believed to be of a vascular nature are sometimes detected, by imaging techniques, fairly early in the course of the dementia, leading to an overdiagnosis of multi-infarct dementia in smokers. Also, a history of smoking could bias towards a diagnosis of multi-infarct dementia whereas a family history of dementia could bias towards an AD diagnosis. Although several epidemiology studies have been done on cigarette smoking and AD, none have been population-based necropsy studies.

The discussion presented in this study poses the confusing question, how does a gene (or genes) increase the incidence of smoking and decrease the incidence of AD but have its effect disappear in MZ twins? Alternatively, a genetic deficiency in central nicotinic cholinergic receptors might diminish the proclivity to smoke and increase the risk for AD. Furthermore, cigarette smoking might upregulate nicotinic cholinergic receptors and thereby protect against the development of AD.[1] We feel that it would be prudent to keep an open mind on the issue of genetic confounding until further data, such as more and better necropsy data, are available.

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1 Smith CJ, Giacobini. Nicotine, Parkinson's and Alzheimer's disease. *Rev Neurosci* 1992; **3:** 25–43.

Authors' reply

SIR—In response to Smith and colleagues we present the following table showing the number of smokers in twin pairs who were discordant for onset of AD:

Proband smoke?	Monozygotic pairs		Dizygotic pairs	
	Co-twin smoke		Co-twin smoke	
	Yes	No	Yes	No
Yes	6	6	8	8
No	3	17	11	8

In such dependent analyses, the informative pairs are those discordant for smoking (top right and bottom left cells).

With respect to diagnoses, we did not exclude individuals with vascular risk factors (including smoking) or apparent mixed dementia (vascular and AD). Instead, we retained these subjects in the categories: possible AD;[1] or dementia of questionable aetiology.[2] When subjects were followed longitudinally with yearly examinations for 2–4 years, some individuals with dementia of questionable aetiology were reassigned to the possible AD or probable AD categories when their illness progressed in typical fashion. So far, the diagnosis of definite AD has been confirmed in all the 15 demented patients who have undergone necropsy (7 with a history of smoking).

With respect to Smith and colleagues last point, we do not suggest that the effect disappears in MZ twins. The effects of the gene (or genes), whatever they may be, will be similar within MZ pairs. Thus, to the extent that the association between smoking and AD is provoked by genetic confounding, a matched comparison of exposures within MZ pairs should no longer show systematic differences (ie, the odds ratio should revert to unity). The mechanism proposed by Smith—ie, a genetic deficiency in central nicotine cholinergic receptors that diminishes proclivity to smoke and simultaneously increases risk of AD—could be an example of genetic confounding. There are undoubtedly others.

Finally, we agree on the importance of keeping an open mind about genetic confounding. We reiterate that careful control of genotype is important for studies of the association between a genetically provoked disease such as AD and environmental factors such as smoking behaviour that might also be under genetic influence.

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1 McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA work group under the auspices of the Department of Health and Human Services task force on Alzheimer's disease. *Neurology* 1984; **34:** 939–44.
2 Breitner JCS, Welsh KA, Robinette CD, Gau BA, Folstein MF, Brandt J. Alzheimer's disease in the National Academy of Sciences Registry of aging twin veterans, II: longitudinal findings in a pilot series. *Dementia* 1994; **5:** 99–105.

Impaired olfactory function in Parkinson's disease

SIR—When James Parkinson published his monograph on shaking palsy he stated that the senses are unimpaired.[1] However, it is becoming increasingly clear that the sense of smell is compromised in Parkinson's disease and furthermore that the loss of olfactory function is independent of motor symptoms, medication, cognitive status, disease duration, and disease severity.[2]

In the course of a larger study, we had the opportunity of assessing both olfactory function and dopamine uptake sites in the striatum by means of single-photon-emission (SPECT) tomography as in patients with Parkinson's disease. We studied the olfactory threshold (1-butanol ascending staircase, 2 bottle, forced-choice method), odour recognition memory for common household odourants (15 min retention interval; 10 old/10 new) and odour identification (20 odourants are to be identified by a multiple-choice four item word list).[3] SPECT was done with the ligand (1231)β-CIT (2-β-carbomethoxy-3-β-(4-iodophenyl)-tropane), a cocaine derivative with high affinity for the dopamine transporter. β-CIT binding in the striatum gives an index of the integrity of dopaminergic nerve endings and is markedly reduced in Parkinson's disease.[4] Results are expressed as the binding ratio striatum cerebellum/cerebellum (specific/ nonspecific binding).