Current cigarette smoking was associated with a higher risk of Alzheimer's disease

Merchant C, Tang MX, Albert S, et al. *The influence of smoking on the risk of Alzheimer's disease. Neurology* 1999 Apr 22;52:1408-12.

Question

Is there an association between cigarette smoking and Alzheimer's disease (AD)?

Design

Cohort analytic study with follow up for a mean of 2 years.

Setting

Community based study in northern Manhattan, New York City, USA.

Participants

1062 elderly Medicare recipients (mean age 75 y, 69% women) without dementia at start of study.

Assessment of risk factors

A structured risk factor questionnaire was developed and used at baseline to determine exposure to putative risk factors related to dementia. 3 sets of questions dealt with smoking history. General health and function, years of formal education, and medical history were determined. A physical, neurological, and neuropsychological examination were also done. *APOE* genotype was determined for each participant.

Main outcome measure

Blinded diagnosis of AD using standardised clinical assessments at annual visits.

Main results

142 participants were diagnosed with AD during follow up. After adjustment for education and ethnicity and using never smoked as the reference, a previous history of smoking was not associated with AD (table). Those who were current smokers had an increased risk of developing AD (table). The association between current smoking and AD decreased in the presence of *APOE* ϵ 4 but not for current smokers without *APOE* ϵ 4 (table).

Conclusions

There was an increased risk of developing Alzheimer's disease among current smokers. *APOE* ϵ 4 slightly modified this association.

Relative risk (RR) of developing Alzheimer's disease by smoking history

Tobacco use	Adjusted RR* (95% CI)
Previous	0.7 (0.5 to 1.1)†
Current	1.7 (1.1 to 2.8)
Current use in <i>APOE</i> ϵ 4 carriers	1.4 (0.6 to 3.3)†
Current use in non- <i>APOE</i> ϵ 4 carriers	2.1 (1.2 to 3.7)

*Multivariate analysis adjusted for education and ethnicity. †Not significant.

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Commentary

The association between smoking and AD is controversial. Several early case control studies suggested that smoking is protective against AD.¹ Because AD is associated with reduced acetylcholine activity, perhaps nicotine delays the disease. These studies, however, may be biased because only very fit smokers, with a genetic advantage, survive into later life.² To some extent, this study by Merchant *et al* and the recently published prospective Rotterdam Study,³ have settled the controversy. Both studies found that present smokers are at roughly double the risk of developing AD than those who have never smoked.

Interestingly, the study by Merchant *et al* (but not the Rotterdam Study) found that former smokers may be at a reduced risk (although the result

was not statistically significant). Because having an *APOE* ϵ 4 allele is a risk factor for developing AD and vascular disease, there may be an interaction between smoking, *APOE* ϵ 4, and AD. Again, both studies found that smoking is more of a risk factor for those without *APOE* ϵ 4. This may reflect, however, the fact that smokers with *APOE* ϵ 4, who survive into later life, are a distinct group.

The main limitation of these studies is that they do not have necropsy confirmation of diagnosis. Smokers may be developing vascular dementia which is misdiagnosed as AD. Also, smoking is a marker for other factors (such as poverty or alcohol use), which Merchant *et al* have tried to take into account by adjusting for education and ethnicity.

The clinical message is do not recommend smoking to any of your patients, at any age. There is some good news for smokers: giving up smoking reduces your risk of developing AD. The bad news is: otherwise smokers can only reduce their risk of AD by dying of something else first.

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- 2 Riggs JE. Smoking and Alzheimer's disease: a protective effect or differential survival bias? *Lancet* 1993;342:793-4.
- 3 Ott A, Slioter AJ, 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.