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Cigarette smoking is a risk factor for Alzheimer's disease: An analysis controlling for tobacco industry affiliation

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Abstract

To examine the relationship between smoking and AD after controlling for study design, quality, secular trend, and tobacco industry affiliation of the authors, electronic databases were searched, 43 individual studies met the inclusion criteria. For evidence of tobacco industry affiliation <http://legacy.library.ucsf.edu> was searched. One fourth (11/43) of individual studies had tobacco affiliated authors. Using random effects meta-analysis, 18 case control studies without tobacco industry affiliation yielded a non-significant pooled odds ratio of 0.91 (95% CI, 0.75–1.10), while 8 case control studies with tobacco industry affiliation yielded a significant pooled odds ratio of 0.86 (95% CI, 0.75–0.98) suggesting that smoking protects against AD. In contrast, 14 cohort studies without tobacco industry affiliation yielded a significantly increased relative risk of AD of 1.45 (95% CI, 1.16–1.80) associated with smoking and the three cohort studies with tobacco industry affiliation yielded a non-significant pooled relative risk of 0.60 (95% CI 0.27–1.32). A multiple regression analysis showed that case-control studies tended to yield lower average risk estimates than cohort studies (by -0.27 ± 0.15 , $P=.075$), lower risk estimates for studies done by authors affiliated with the tobacco industry (by -0.37 ± 0.13 , $P=.008$), no effect of the quality of the journal in which the study was published (measured by impact factor, $P=0.828$), and increasing secular trend in risk estimates ($0.031/\text{year} \pm 0.013$, $P=.02$). The average risk of AD for cohort studies without tobacco industry affiliation of average quality published in 2007 was estimated to be 1.72 ± 0.19 ($P<.0005$). The available data indicate that smoking is a significant risk factor for Alzheimer's disease.

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INTRODUCTION

In 2006, there were 26.6 million people with Alzheimer's disease (AD). AD prevalence will quadruple by 2050, increasing the burden of care and the associated health costs.[1] Cardiovascular disease is a major risk factor for AD[2] and smoking cigarettes causes cardiovascular disease.[3,4] Despite a growing body of evidence linking smoking with AD, [5–8] beliefs prevail that smoking protects against AD in both scholarly journals and lay publications.[9–13] For example, a 2008 study of nicotine dependence in *Human Genetics* begins with the statement, “epidemiological studies reveal that cigarette smoking is inversely associated with AD”[14] the “Alzheimer's Disease Facts and Figures,”[15] published by the Alzheimer's Association, does not mention smoking and the May 8, 2008 *Oprah Magazine*, a trusted source of health information for millions of women, reported that nicotine might protect people from AD.[16] As of October 2008, over 100 web sites stated that smoking was protective for AD. Confusion regarding the role of smoking in AD may discourage cessation attempts among older smokers and contribute to the reluctance of health care providers to treat tobacco dependence in older smokers.[17] A delay in AD onset or progression by just one year would result in nearly 9.2 million fewer cases in 2050.[1] There is a pressing need to understand the risk factors for AD, particularly clarification of smoking's effect.

Previous reviews[5–13,18] of the association between smoking and AD have not controlled for both study design and author affiliation with the tobacco industry. In 2002, Almeida et al.[5] identified study design (cohort or case-control) as an important methodological issue because of survival and recall bias that may be responsible for the unclear direction of the association between smoking and AD. But, at the time, only four cohort studies were available, and the direction of the association remained unclear.[5] In 2007, Anstey et al.[6] published a meta-analysis of 19 cohort studies and found that, compared with people who had never smoked, current smokers had an increased risk of AD. Hernan et al.[7] identified 12 prospective studies and found a wide range of risks for AD associated with smoking, which they attributed to bias due to censoring by death. Purnell's[8] 2008 systematic review of cardiovascular risk factors and incident AD reported on only four cohort studies that used incident cases of AD, three of which reported that current smoking increased the risk of AD and one found no significant relationship.

As early as 1976, the tobacco industry began to invest in AD research,[19,20] with the goal of developing nicotine-related diagnostics and therapeutics.[21] These research efforts were conducted through the industry's Council for Tobacco Research (CTR) and the individual tobacco companies (RJ Reynolds [RJR] Biomedical Research Program[19,20] and Philip Morris Research[22]). CTR's interest in AD started in 1981 following published anecdotal observations of low rates of tobacco use among patients with AD.[23,24] In 1987, RJR's “Smoking and Health's contract program” identified several key research areas, including the “possible relationships between smoking and Alzheimer's Disease.”[25] In 1993, Philip Morris' interests in AD research were to “not only understand the role of smoking in this disorder but also provide early diagnostics ... as well as potential therapeutics (e.g., nicotine analogs).”[21]

Past research has shown that the tobacco industry funding of research on the health risks of smoking is associated with findings that support their position. For example, research

showing that factors like genetics, personality type or aging were responsible for diseases such as lung cancer and cardiovascular disease.[26–28] Industry sponsored research is more likely to reach conclusions that are favorable to the sponsor and experience publication bias, publication delays and data withholding.[29] This has been true for sponsorship not only from the tobacco industry[30,31] but also from the pharmaceutical[32,33] and chemical industries.[34] The present systematic review estimates the association between cigarette smoking and AD after controlling for study design, quality, secular trend and tobacco industry affiliation of the authors.

MATERIALS AND METHODS

Identification of Relevant Research Publications

We searched PubMed, PsycINFO, Google Scholar, and Cochrane CENTRAL for reviews and individual studies published as full articles or brief reports using combinations of keywords for smoking (smoking, tobacco, cigarettes and nicotine) and AD (Alzheimer's disease, dementia, cognition, cognitive impairment, vascular dementia). We also examined reference lists of prior reviews and individual studies and contacted experts in the field. For inclusion, studies needed to be published, use AD as the outcome (not dementia or cognitive decline), human subjects (brain tissue excluded), a measurement of smoking (i.e., ever smoker, current smoker, never smoker), and have a clearly stated study design (case-control or cohort). One prevalence study[35] was included and coded as a case-control study. If both raw and adjusted risk ratios were available, ratios adjusted for the most covariates were used.

The initial search returned 336 articles; 47 met the requirement for detailed review, of which 43 original research studies met our inclusion criteria (Table 1 and Table 2 and Figure 1). One publication was excluded because it was a letter to the editor and the criteria used for diagnosis of AD were unclear.[36] One other publication was excluded[37] because results from the same study were published in two papers, and we included the more completely reported results.[38] For multiple publications from the same sample with the same smoking measures, we used the publication with the longest follow-up; in particular, for the Rotterdam Study, the latest 2007 report[39] was chosen over the 1998 report[40] and for the Canadian Study of Health and Aging the 2002 report[41] was chosen over the three previous reports.[42–44] When the studies were stratified by race,[45,46] results for the separate populations were included as separate studies. A paper by Wang (1999) provided both case-control and cohort results, which also were treated as separate studies.[47]

For each study, we recorded the smoking exposure measure, method of diagnosing AD and covariates. For each case-control study, we recorded the number of cases and controls, the number of cases and controls who smoked, the source of cases and controls, and multivariate odds ratio (OR) and 95% confidence interval and *P* value (Table 1). For each cohort study, we recorded the size and source of the cohort, years of follow-up, covariates, multivariate relative risk (RR), and confidence interval (Table 2).

Ten of the 43 studies were reviewed by two individuals, one reviewer blinded to author, journal, and publication date; there was 100% agreement.

We also identified 10 systematic reviews (Table 3).

Tobacco Documents Research

We searched the Legacy Tobacco Documents Library for evidence of tobacco industry affiliation of the studies' authors (<http://legacy.library.ucsf.edu>), a collection of over 51 million pages of previously secret internal documents from the major tobacco companies

and organizations that were made available as a result of litigation against the tobacco industry.[48,49] Tobacco industry affiliation was defined as current or past funding, employment, paid consultation, collaboration, or co-authorship on the included study with someone with then-current or previous tobacco industry funding (within ten years of publication).

The search for possible tobacco industry affiliations was conducted from July 2006 to July 2008 using keywords “Alzheimer’s disease,” “dementia,” “cognition,” and the names of authors and university affiliations of the AD studies in this meta-analysis. Expanded searches were conducted using information in initially identified documents, including named individuals, specific programs, and dates and reference (Bates) numbers. Initial searches produced 10,798 documents. After screening documents based on index entries, we identified 3,324 documents to review. After eliminating duplicates and irrelevant documents, we analyzed 877 documents.

Statistical Analyses

In our meta-analysis we analyzed cohort studies (which yield direct estimates of relative risk) and case control studies (which yield odds ratios) separately. We tested for heterogeneity with the Q test statistic. Random effects meta-analysis was used to estimate pooled risk ratios and 95% confidence limits using the DerSimonian and Laird method because of observed heterogeneity among results among the cohort studies[50] (Stata 10.1 metan). We used Begg’s funnel plot to test for publication bias (Stata metabias).

We tested for the effect of study design, quality, secular trend and tobacco industry affiliation in a weighted (using weights from the meta-analysis using Stata regress option pweight) multiple regression analysis in which the dependent variable was the point estimate of the risk of AD and the independent variables were study design (0=case control, 1=cohort), study quality indexed as the impact factor of the journal (in 2009), where the study was published, secular trend (measured as year of publication, setting 2007 as 0) and tobacco industry affiliation (0=no, 1=yes). We selected 2007 as the base year because that was the year of the most recent individual study. Doing so gives the constant in the regression equation the following interpretation: The average risk estimate one would predict for a cohort study published in 2007 in an average quality journal by a group without tobacco industry affiliation. The choice of base year has no effect on the values, standard errors, or statistical significance of the predictor variables in the model.

Because the type of study design and likelihood of tobacco industry affiliation may have changed systematically over time, we computed variance inflation factors to test for collinearity in the independent variables in the regression analysis. We tested whether the model assumptions were met (linearity of the dependent variable and normality of error terms) by examining a normal probability plot of the residuals.

For review papers, we tested for a significant association between author affiliation with the tobacco industry and the conclusion of their review using a two tailed Fisher Exact Test, with reviews dichotomized into “protective” or “not protective or ambiguous.”

RESULTS

Individual Studies and Meta-Analysis

There was no evidence of publication bias (Figure 2).

Of the 43 individual studies of smoking and AD (Figure 1), 26 were case-control studies (Table 1) and 17 were cohort studies (Table 2). Eleven of the 43 studies (26%) were

conducted by tobacco industry affiliated investigators. Out of 11 tobacco affiliated studies only 3 disclosed an affiliation (27%). Of the 8 case control studies with tobacco affiliation, just 3 disclosed the affiliation (37%); of the 3 cohort studies with tobacco affiliation, none disclosed the affiliation.

The 18 case-control studies without tobacco industry affiliation yielded a nonsignificant pooled odds ratio of 0.91 (95% CI 0.75–1.10; Table 1 and Figure 1). In contrast, the 8 case-control studies with tobacco industry affiliation yielded a significant pooled odds ratio of 0.86 (95% CI 0.75–0.98; Table 1 and Figure 1), suggesting that smoking protects against AD. The 14 cohort studies without tobacco industry affiliation indicated a significantly increased relative risk of AD of 1.45 (95% CI 1.16–1.80; Table 2 and Figure 1) associated with smoking. In contrast, the three cohort studies with tobacco industry affiliation yielded a non-significant pooled relative risk of 0.60 (95% CI 0.27–1.32; Table 2 and Figure 1).

Table 3 presents the results of the multiple regression analysis that estimates the simultaneous effects of study design, study quality, secular trend and tobacco industry affiliation. Controlling for the other variables, on the average case-control studies tended to yield lower risk estimates than cohort studies (by $-.27$, $P=.075$). Study quality, measured by the impact factor of the journal in which the paper was published, was not associated with the magnitude of the risk estimate ($P=.828$). There was a secular trend in risk estimates, with the newer studies showing higher risks (increasing at $0.031/\text{year}$, $P=.020$). Controlling for these other factors, affiliation with the tobacco industry was associated with significantly lower risk estimates, by $-.37$ ($P=.008$). Controlling for these other factors, this analysis indicates that the average risk of AD based on a non-industry affiliated cohort study in 2007 is 1.72 ($P<.0005$, the constant in the regression equation). All the variance inflation factors were 1.39 or less, indicating that these different factors were independent of each other.

Systematic Reviews

Ten systematic reviews of the association between smoking and AD were published between 1992 and 2008 (Table 4); 4 had tobacco industry affiliated authors. The association between author affiliation with the tobacco industry and the conclusion of their review was significant ($P=0.005$). Among the 6 reviews without tobacco industry affiliation, 1 found “no clear effect,” [9] 2 found “no protective effect” of smoking for AD,[5,18] and 3 found smoking to be a significant risk factor for AD.[6–8] The 4 reviews with known tobacco industry affiliation concluded that smoking “protected against AD.”[10–13]

DISCUSSION

Controlling for study design, quality, secular trend and tobacco industry affiliation, we found a significant increase in AD risk associated with smoking. Controlling for all these factors, current or ever tobacco smoking was a significant risk factor for AD ($RR=1.72$; 95% CI 1.33–2.12 for cohort studies of average quality in 2007). Case-control studies tended to yield lower risks than cohort studies and most of the tobacco affiliated studies used case-control design. Even after controlling for study design, tobacco industry affiliation was independently associated with lower risk estimates. In contrast to the significant increase in risk of AD that our analysis demonstrated, the combination of case-control design and tobacco industry affiliation yielded a protective odds ratio of 0.86 (95% CI 0.75–0.98).

The need to account for these factors in evaluating the evidence is demonstrated by the fact that if one simply combined all 43 studies in a single random effects meta-analysis, one would obtain an inaccurate null result (risk ratio = 1.05; 95% CI 0.91–1.20).

In 1992, Hirayama et al.[51] (no tobacco affiliation), published the first large cohort study and found smoking to be a risk factor for AD (RR = 1.61; 95% CI 1.10–2.38). In reference to Hiriyama's soon to be published paper, PN Lee a long-time, paid statistical consultant for the tobacco industry,[52–54] informed Philip Morris Tobacco Company in a secret report, that “prospective studies are often more scientifically valid than case-control studies.”[55] However, Philip Morris continued to fund case-control studies and in 1994, RJR Biological Research Division initiated a project to investigate the “Utility and Feasibility of Funding Epidemiology Studies on smoking and Alzheimer's Disease.”[56] This project included a review of current literature and several interviews with tobacco industry affiliated scientists. The recommendation from this project was that, it was no longer “feasible... to fund either a prospective or retrospective epidemiology study on cigarette smoking and AD.”[56]

In an earlier review of AD and smoking studies, cohort designs were found to be less susceptible to bias than case-control designs.[57] A potential problem with case-control studies is recall bias. AD patients all have memory deficits and reports given by proxy are often used to obtain smoking history. However, if proxy reports are not used for the control subjects as well, then bias can result.[57] Differential mortality is a problem when investigating the effects of smoking in Alzheimer's disease because of the very low incidence rates of AD before age 75.[58] Persons with AD often die more quickly and are unavailable for case-control studies, which may lead to the false interpretation that smoking among cases is less common than it actually is and that smoking among control subjects is more common than among cases. Cohort studies often involve only a short time period of only 3–5 years, whereas, case control studies may cover activities over a period of decades. Debanne et al.[59] conducted a simulation study that showed that cohort studies also understate the risk of AD in smokers because of early deaths. (They did not compare the magnitude of the bias in cohort vs. case-control studies.) When survival among persons with the disease is related to the exposure of interest, downward bias can result.[57]

Limitations

Our study has several limitations. The primary data collector (JKC) was not blinded. The data extracted, however, were objective (i.e., risk ratios). In a study of blinding in 5 meta-analyses, blinding made no difference in the pooled risk estimates.[60]

In the document search for tobacco industry affiliation, we may not have retrieved every relevant document. Some materials may have been destroyed or concealed by the tobacco companies.[61] After 1998, the tobacco companies were aware that documents might eventually be made public and became more careful about what they wrote down.[62]

The application of meta-analysis to observational studies can be problematic because of biases in both the original studies and publication bias.[57,63,64] There is, however, no evidence of publication bias in the studies we considered (Figure 2).

Random effects meta-analysis is considered the appropriate approach for estimating risks when there are heterogeneous results among studies,[50] but does not explain the reasons for this heterogeneity. By dividing the studies according to design type (case-control or cohort) and whether or not there was tobacco industry affiliation, we found both groups of case-control studies to be homogenous. Both groups of cohort studies remained heterogeneous (albeit less so); we did not explore the reasons for heterogeneity within these subsets of studies. Study design type, industry affiliation and year of publication explained a significant portion of the heterogeneity among the 43 studies.

There was a nonsignificant trend toward lower risk estimates being associated with case-control studies (which yield ORs) than cohort studies (which yield RRs). The OR is an

estimate of the RR when the RR is near 1.0; to the extent that the ORs from the case-control studies are not good estimates of the RR, this coefficient in the regression model (Table 3) quantifies the net effect of differences in results due to study design and biases due to using the OR as an estimate of RR.

One should interpret this significant association between conclusions of systematic reviews and tobacco industry affiliation cautiously. In the individual studies there is a secular trend in publishing, type of design, and tobacco industry funding, which may be confounded in this analysis of the reviews. There is a clear time trend in the publishing of case-control and cohort studies, with more of the former appearing in earlier years. Specifically, of the 26 case-control studies in Table 1, 23% were published in the 1980s, 58% in the 1990s, and 19% in the 2000s. In contrast, of the 17 cohort studies in Table 2, 6% were published in the 1980s, 41% in the 1990s, and 53% in the 2000s. It could be possible that the year of publication is associated with the conclusion of a reduction in AD risk for smokers, since all the industry-affiliated reviews were published in 1994 or earlier. This finding may be also be due to the fact that the tobacco industry stopped supporting reviews after 1994, as the cohort studies were beginning to appear.[56]

Conclusion

For the last two decades, the tobacco industry has been actively funding research that supports the position that cigarette smoking protects against AD, and for the past two decades, the scientific literature has reported conflicting results as to the direction of the association between smoking and AD. Consequently, older smokers and their health care providers have been unaware that smoking is a modifiable risk factor for AD. There is an association between tobacco industry affiliation and the conclusions of individual studies and, probably, review papers of AD. Controlling for industry affiliation, study design and other factors, smoking is not protective against AD; it is a significant and substantial risk factor for Alzheimer's disease.

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References

1. Brookmeyer R. Forecasting the global prevalence and burden of Alzheimer's disease. *Alzheimers Dement.* 2007; 3:186–191. [PubMed: 19595937]
2. Meyer JS, Rauch GM, Rauch RA, Haque A, Crawford K. Cardiovascular and other risk factors for Alzheimer's disease and vascular dementia. *Annal N Y Acad Science.* 2000; 903:411–423.
3. Bazzano LA, He J, Muntner P, Vupputuri S, Whelton PK. Relationship between cigarette smoking and novel risk factors for cardiovascular disease in the United States. *Ann Intern Med.* 2003; 138:891–897. [PubMed: 12779299]
4. Ockene IS, Miller NH. Cigarette smoking, cardiovascular disease, and stroke a statement for healthcare professionals from the American Heart Association. *Circulation.* 1997; 96:3243–3247. [PubMed: 9386200]
5. Almeida OP, Hulse GK, Lawrence D, Flicker L. Smoking as a risk factor for Alzheimer's disease: contrasting evidence from a systematic review of case-control and cohort studies. *Addiction.* 2002; 97:15–28. [PubMed: 11895267]

6. Anstey KJ, von Sanden C, Salim A, O'Kearney R. Smoking as a risk factor for dementia and cognitive decline: a meta-analysis of prospective studies. *Am J Epidemiol.* 2007; 166:367–378. [PubMed: 17573335]
7. Hernan MA, Alonso A, Logroscino G. Cigarette smoking and dementia: potential bias in the elderly. *Epidemiology.* 2008; 19:448–450. [PubMed: 18414087]
8. Purnell C, Gao S, Callahan CM, Hendrie HC. Cardiovascular risk factors and incident Alzheimer disease. *Alz Dis Assoc Dis.* 2008
9. Fratiglioni L, Wang HX. Smoking and Parkinson's and Alzheimer's disease: review of the epidemiological studies. *Behav Brain Res.* 2000; 113:117–120. [PubMed: 10942038]
10. Graves AB. EURODEM Risk Factors Research Group. Alcohol and tobacco consumption as risk factors for Alzheimer's disease: a collaborative re-analysis of case-control studies. *Int J Epidemiol.* 1991; 20:48–57.
11. Lee PN. Smoking and Alzheimer's disease: a review of the epidemiological evidence. *Environ Tech Lett.* 1994; 13:131–144.
12. Smith CJ, Giacobini E. Nicotine, Parkinson's and Alzheimer's disease. *Rev. Neurosci.* 1992; 3:25–43. [PubMed: 21561277]
13. van Duijn CM, Clayton DG, Chandra V, Fratiglioni L, Graves AB, Heyman A, Jorm AF, Kokmen E, Kondo K, Mortimer JA. EURODEM Risk Factors Research Group. Interaction between genetic and environmental risk factors for Alzheimer's disease: a reanalysis of case-control studies. *Genet Epidemiol.* 1994; 11:539–551. [PubMed: 7713394]
14. Chen GB, Payne TJ, Lou XY, Ma JZ, Zhu J, Li MD. Association of amyloid precursor protein-binding protein, family B, member 1 with nicotine dependence in African and European American smokers. *Hum Genet.* 2008 ISSN 0340-6717.
15. Alzheimer's Association. Alzheimer's disease facts and figures. [September 16, 2008, Accessed]. www.alz.org/national/documents/report_alzfactsfigures2008.pdf
16. Barr, N. Oprah Magazine. Harpo, Publications; 2008.
17. Cataldo JK. Clinical implications of smoking and aging: breaking through the barriers. *J Gerontol Nurs.* 2007; 33:32–41. [PubMed: 17718376]
18. Turner C, Spilich GJ. Research into smoking or nicotine and human cognitive performance: does the source of funding make a difference? *Addiction.* 1997; 92:1423–1426. [PubMed: 9519485]
19. Biomedical Research Contributions 00 1976. RJ Reynolds:
<http://legacy.library.ucsf.edu/tid/nfw92d00>
20. Seitz, F. Report on R. J. Reynolds Research Grants Program. RJ Reynolds: [06 Aug 1981].
<http://legacy.library.ucsf.edu/tid/njs65d00>
21. Carchman, RA. Case Western. Philip Morris: [29 Sep 1993].
<http://legacy.library.ucsf.edu/tid/xzn87e00>
22. Carchman, RA. Proposed Alzheimers' Study Status. Philip Morris: [24 Sep 1990].
<http://legacy.library.ucsf.edu/tid/tpc58e00>
23. Ford, D. Site visit to Dr. L. Barclay at the Burke Rehabilitation Center, White Plains, New York, February 20, 1987 site visitors: Drs. D.H. Ford and H. McAllister grant no. 1965 Tobacco use in relation to Alzheimer's disease 00 1987. Council for Tobacco Research.
<http://legacy.library.ucsf.edu/tid/gfb79c00>
24. Appel, SH. Alzheimer's Disease. In: Enna, SJ., editor. *Brain neurotransmitters and receptors in aging and age related disorders.* New York City: Raven Press; 1981.
25. Status Report on Key R&D Programs Year-End. RJ Reynolds: 1987 [09 Feb 1988]. (870000)
<http://legacy.library.ucsf.edu/tid/gtx54d00>
26. Glantz, SA.; Slade, J.; Bero, LA.; Hanauer, P.; Barnes, D. *The cigarette papers.* Berkeley: The University of California Press; 1996.
27. Bero LA. Tobacco industry manipulation of research. *Public Health Rep.* 2005; 120:200–208. [PubMed: 15842123]
28. Bero LA, Glantz S, Hong MK. The limits of competing interest disclosures. *Tob Control.* 2005; 14:118–126. [PubMed: 15791022]

29. Bekelman JE, Li Y, Gross CP. Scope and impact of financial conflicts of interest in biomedical research: a systematic review. *JAMA*. 2003; 289:454–465. [PubMed: 12533125]
30. Barnes DE, Bero LA. Why review articles on the health effects of passive smoking reach different conclusions. *JAMA*. 1998; 279:1566–1570. [PubMed: 9605902]
31. Scollo M, Lal A, Hyland A, Glantz S. Review of the quality of studies on the economic effects of smoke-free policies on the hospitality industry. *Tobacco Control*. 2003; 12:13–20. [PubMed: 12612356]
32. Cho MK, Bero LA. The quality of drug studies published in symposium proceedings. *Ann Int Med*. 1996; 124:485–489. [PubMed: 8602706]
33. Lexchin J, Bero LA, Djulbegovic B, Clark O. Pharmaceutical industry sponsorship and research outcome and quality: systematic review. *Brit Med J*. 2003; 326:1167–1170. [PubMed: 12775614]
34. Swaen GM, Meijers JM. Influence of design characteristics on the outcome of retrospective cohort studies. *Brit J Ind Med*. 1988; 45:624–629. [PubMed: 3179238]
35. Bowirrat A, Treves TA, Friedland RP, Korczyn AD. Prevalence of Alzheimer's type dementia in an elderly Arab population. *Eur J Epidemiol*. 2001; 8:119–123.
36. Grossberg GT, Nakra R, Woodward V, Russell T. Smoking as a risk factor for Alzheimer's disease. *J AM Geriatr Soc*. 1989; 37:819. [PubMed: 2754163]
37. Salib E. Risk factors in clinically diagnosed Alzheimer's disease: a retrospective hospital-based case control study in Warrington. *Aging & Mental Health*. 2000; 4:259–267.
38. Salib E, Hillier V. A case-control study of smoking and Alzheimer's Disease. *Int J Geriatr Psychiat*. 1997; 12:295–300.
39. Reitz C, den Heijer T, van Duijn C, Hofman A, Breteler MMB. Relation between smoking and risk of dementia and Alzheimer disease: The Rotterdam Study. *Neurology*. 2007; 69:998–1105. [PubMed: 17785668]
40. Ott A, Slioter AJ, Hofman A, van Harskamp F, Witteman JC, Van Broeckhoven C, van Duijn CM, Breteler MM. Smoking and risk of dementia and Alzheimer's disease in a population-based cohort study: the Rotterdam Study. *Lancet*. 1998; 351:1840–1843. [PubMed: 9652667]
41. Lindsay J. Risk factors for Alzheimer's disease: a prospective analysis from the Canadian Study of Health and Aging. *Am J Epidemiol*. 2002; 156:445–453. [PubMed: 12196314]
42. Andel R. The Canadian Study of Health and Aging: risk factors for Alzheimer's disease in Canada. *Neurology*. 1994; 44:2073–2080. [PubMed: 7969962]
43. Tyas SL. Alcohol Use and the Risk of Developing Alzheimer's Disease. 2001; 25:299–307.
44. Tyas SL, Koval JJ, Pederson LL. Does an interaction between smoking and drinking influence the risk of Alzheimer's disease? Results from three Canadian data sets. *Stat Med*. 2000; 19:1685–1696. [PubMed: 10844727]
45. Bachman DL, Green RC, Benke KS, Cupples LA, Farrer LA. Comparison of Alzheimer's disease risk factors in white and African American families. *Neurology*. 2003; 60:1372–1374. [PubMed: 12707449]
46. Harwood DG, Barker WW, Loewenstein DA, Ownby RL, St. George-Hyslop P, Mullan M, Duara R. A cross-ethnic analysis of risk factors for AD in white Hispanics and white non-Hispanics. *Neurology*. 1999; 52:551–551. [PubMed: 10025786]
47. Wang HX, Fratiglioni L, Frisoni GB, Viitanen M, Winblad B. Smoking and the Occurrence of Alzheimer's Disease: Cross-Sectional and Longitudinal Data in a Population-based Study. *Amer J Epidemiol*. 1999; 149:640–644. [PubMed: 10192311]
48. Bero L. Implications of the tobacco industry documents for public health and policy. *Annu Rev Publ Health*. 2003; 24:267–288.
49. Malone RE, Balbach ED. Tobacco industry documents: treasure trove or quagmire? *Tob Control*. 2000; 9:334–338. [PubMed: 10982579]
50. Sutton, AJ.; Abrams, KR.; Jones, DR.; Sheldon, TA.; Song, F. *Methods for Meta-Analysis in Medical Research*. New York: Wiley; 2000.
51. Hirayama T. Large cohort study on the relation between cigarette smoking and senile dementia without cerebrovascular lesions. *Brit Med J*. 1992; 1:176.

52. Lee, PN. Reanalysis of Prof. V.M. Hawthorne's Data Some Comments on the Report by Liesi Hebert and John Fry (Td 1659). Philip Morris: [08 Oct 1982]. <http://legacy.library.ucsf.edu/tid/xhj32e00>
53. Lee, PN. Misclassification of Smoking Habits and Its Relevance to the Observed Relationship between Passive Smoking and Lung Cancer a Review of the Evidence. Philip Morris: [04 Jun 1987]. <http://legacy.library.ucsf.edu/tid/aoy68e00>
54. Lee, PN. Subject Index of Reviewed Papers on Smoking and Health from 780000. Philip Morris: [00 Feb 1995]. <http://legacy.library.ucsf.edu/tid/crg22d00>
55. Lee, PN. Brit Med J. Vol. 302. Philip Morris: [12 Aug 1991]. Subject Ref 18a 'Relation between Nicotine Intake and Alzheimer's Disease Cm Van Duijn and a Hofman; p. 1491-1494.(910000) <http://legacy.library.ucsf.edu/tid/hcu34e00>
56. Utility and Feasibility of Funding Epidemiology Studies on Smoking and Alzheimer's Disease (Ad). RJ Reynolds: [06 Jan 1994]. Biological Research and Debethizy JD. RDM CJS94 001. <http://legacy.library.ucsf.edu/tid/wex53d00>
57. Kukull WA. The association between smoking and Alzheimer's disease: effects of study design and bias. Biol Psychiat. 2001; 49:194–199. [PubMed: 11230870]
58. Wolf-Klein GP, Silverstone FA, Brod MS, Levy A, Folety C, Termotto V, Breuer J. Are Alzheimer patients healthier? J Amer Geriatr Soc. 1988; 36:219–224. [PubMed: 3339230]
59. Debanne S, Bielefeld R, Cheruvu V, Fritsch T, Rowland D. Alzheimer's disease and smoking: bias in cohort studies. J Alzheimers Dis. 2007; 11:313–321. [PubMed: 17851182]
60. Berlin JA. Does blinding of readers affect the results of meta-analyses? Lancet. 1997; 350:185–186. [PubMed: 9250191]
61. Liberman J. The shredding of BAT's defense: McCabe v British American Tobacco. Aust Tob Control. 2002; 11:271–274.
62. LeGresley E, Muggli M, Hurt R. Playing hideandseek with the tobacco industry. Nicotine Tob Research. 2005; 7:27–40.
63. Blettner M, Sauerbrei W, Schlehofer B, Scheuchenpflug T, Friedenreich C. Traditional reviews, meta-analyses and pooled analyses in epidemiology. Int J Epidemiol. 1999; 28:1–9. [PubMed: 10195657]
64. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB. Meta-analysis of Observational Studies in Epidemiology A Proposal for Reporting. JAMA. 2000; 283:2008–2012. [PubMed: 10789670]
65. Amaducci LA. Risk factors for clinically diagnosed Alzheimer's disease: a case-control study of an Italian population. Neurology. 1986; 36:922–931. [PubMed: 3714054]
66. Brenner DE. Relationship between cigarette smoking and Alzheimer's disease in a population-based case-control study. Neurology. 1993; 43:293–300. [PubMed: 8437692]
67. Broe GA. A case-control study of Alzheimer's disease in Australia. Neurology. 1990; 40:1698–1707. [PubMed: 2146525]
68. Chandra V. Case-control study of late onset" probable Alzheimer's disease". Neurology. 1987; 37:1295–1300. [PubMed: 3614650]
69. Debanne SM, Rowland DY, Riedel TM, Cleves MA. Association of Alzheimer's disease and smoking: the case for sibling controls. J Amer Geriatr Soc. 2000; 48:800–806. [PubMed: 10894320]
70. Ferini-Strambi I, Smirne S, Garancini P, Pinto P, Franceschi M. Clinical and epidemiological aspects of Alzheimer's disease with presenile onset: a case control study. Neuroepidemiology. 1990; 9:39–49. [PubMed: 2330070]
71. Forster DP, Newens AJ, Kay DW, Edwardson JA. Risk factors in clinically diagnosed presenile dementia of the Alzheimer type: a case-control study in northern England. J Epidemiol Comm Health. 1995; 49:253–258.
72. French LR, Schuman LM, Mortimer JA, Hutton JT, Boatman RA, Christians B. A case-control study of dementia of the Alzheimer type. Am J Epidemiol. 1985; 121:414–421. [PubMed: 4014131]
73. Heyman A, Wilkinson WE, Stafford JA, Helms MJ, Sigmon AH, Weinberg T. Alzheimer's disease: A study of epidemiological aspects. Ann Neurol. 1984; 15:335–341. [PubMed: 6742780]

74. Maia L, de Mendonca A. Does caffeine intake protect from Alzheimer's disease? *Eur J Neurol*. 2002; 9:377–382. [PubMed: 12099922]
75. Prince M. Risk factors for Alzheimer's disease and dementia: a case-control study based on the MRC elderly hypertension trial. *Neurology*. 1994; 44:97–104. [PubMed: 8290099]
76. Shaji S, Promodu K, Abraham T, Roy KJ, Verghese A. An epidemiological study of dementia in a rural community in Kerala, India. *Brit J Psychiat*. 1996; 168:745.
77. Shalat SL, Seltzer B, Pidcock C, Baker E. Risk factors for Alzheimer's disease: A case-control study. *Neurology*. 1987; 37:1630–1633. [PubMed: 3658170]
78. van Duijn CM, Hofman A. Relation between nicotine intake and Alzheimer's disease. *Brit Med J*. 1991; 302:1491–1494. [PubMed: 1855016]
79. Wang PN, Wang SJ, Hong CJ, Liu TT, Fuh JL, Chi CW, Liu CY, Liu HC. Risk factors for Alzheimer's disease: a case-control study. *Neuroepidemiology*. 1997; 16:234–240. [PubMed: 9346343]
80. Friedland, RP. Philip Morris: [07 Feb 2000]. R582 <http://legacy.library.ucsf.edu/tid/pir17d00>
81. Friedland RP, Farrer LA, Cupples LA, Debanne SM, Lerner AJ. MIRAGE Study Group. Smoking and risk of Alzheimer's disease. *Lancet*. 1998; 352:819. [PubMed: 9737315]
82. Friedland RP, Fritsch T, Smyth KA, Koss E, Lerner AJ, Chen CH, Petot GJ, Debanne SM. Patients with Alzheimer's disease have reduced activities in midlife compared with healthy control-group members. *Arch Neurol*. 2001; 60:753–759. [PubMed: 12756140]
83. Barclay, LBRC. Council for Tobacco Research. [27 Dec 1985]. <http://legacy.library.ucsf.edu/tid/geb79c00>
84. Information Required for Drawing and Mailing of CTR Grant Checks. 00 1900. Council for Tobacco Research. <http://legacy.library.ucsf.edu/tid/tcb79c00>
85. Gertenbach, RFCTR. Council for Tobacco Research. [10 Mar 1986]. Grant No. 1965. <http://legacy.library.ucsf.edu/tid/tdb79c00>
86. Bowirrat, A.; Chapman, J.; Friedland, RP.; Hofman, A.; Iqbal, K.; Korczyn, AD.; Snider, A.; Swaab, DF.; Treves, T.; Winblad, B.; Wisniewski, HM. Alzheimer's Disease Prevalence Is High in Israeli Arabs. Philip Morris: The 6th International Conference on Alzheimer's Disease and Related Disorders. 00 1998. <http://legacy.library.ucsf.edu/tid/yhs34a00>
87. Budget Justification Molecular and Cultural Epidemiology of Alzheimer's Disease and Related Disorders: Israel - Cleveland Collaborative Studies. Philip Morris: 00 1997. <http://legacy.library.ucsf.edu/tid/iot08d00>
88. Graves AB, White E, Koepsell TD, Reifler BV, van Belle G, Larson EB, Raskind M. A case-control study of Alzheimer's disease. *Ann Neurol*. 1990; 28:766–774. [PubMed: 2285263]
89. Molecular and Cultural Epidemiology of Ad and Related Disorder: Israel - Cleveland Collaborative Studies. Philip Morris: [21 Mar 1996]. <http://legacy.library.ucsf.edu/tid/aem13e00>
90. Graves, AB. Philip Morris: [20 Mar 1996]. <http://legacy.library.ucsf.edu/tid/cem13e00>
91. Lerner A, Koss E, Debanne S, Rowland D, Smyth K, Friedland R. Smoking and oestrogen-replacement therapy as protective factors for Alzheimer's disease. *Lancet*. 1997; 349:403–404. [PubMed: 9033479]
92. Philip Morris: [18 Jun 1997]. R582. <http://legacy.library.ucsf.edu/tid/ouq17d00>
93. Budget Justification the CWRU- AD Case-Control Study. Philip Morris: 00 1997. <http://legacy.library.ucsf.edu/tid/lot08d00>
94. Plassman BL, Helms MJ, Welsh KA, Saunders AM, Breitner JC. Smoking, Alzheimer's disease, and confounding with genes. *Lancet*. 1995; 345:387. [PubMed: 7772122]
95. Contract Information. RJ Reynolds: [20 Dec 1993]. <http://legacy.library.ucsf.edu/tid/wwg92d00>
96. Duke, U.; Levin, ED. Analysis of the Interactions of Smoking and Alzheimer's Disease. RJ Reynolds: [16 Dec 1993]. <http://legacy.library.ucsf.edu/tid/ywg92d00>
97. Friedland, RP. Philip Morris: [29 Jan 1993]. <http://legacy.library.ucsf.edu/tid/qci48e00>
98. RJR; Ehmann, CW.; Rjhn, I.; Levin, ED.; Snyderman, R.; Duke, U. Described in the Basic Research Proposals Entitled "Analysis of the Interactions of Smoking and Alzheimer's Disease", "Use of Transdermal Nicotine for Treatment of Alzheimer's Disease", and "Critical Sites of Action for Nicotine-Induced Cognitive Improvement". RJ Reynolds: [16 Dec 1993]. This Will Confirm to

You That R.J. Reynolds Tobacco Company ("Reynolds") Will Support Nicotine Research Which You Are Conducting, through a Gift to Duke University Medical Center (the "Institution"). <http://legacy.library.ucsf.edu/tid/xwg92d00>

99. Nordberg, AUU.; Winblad, BUU.; Neuroscience, L. Reduced Number of (3h) Nicotine and (3h) Acetylcholine Binding Sites in the Frontal Cortex of Alzheimer Brains. Council for Tobacco Research. 00 1986. <http://legacy.library.ucsf.edu/tid/fxw46d00>
100. Aggarwal NT, Bienias JL, Bennett DA, Wilson RS, Morris MC, Schneider JA, Shah RC, Evans DA. The Relation of Cigarette Smoking to Incident Alzheimer's Disease in a Biracial Urban Community Population. *Neuroepidemiology*. 2006; 26:140–146. [PubMed: 16493200]
101. Broe GA, Creasey H, Jorm AF, Bennett HP, Casey B, Waite LM, Grayson DA, Cullen J. Health habits and risk of cognitive impairment and dementia in old age: a prospective study on the effects of exercise, smoking and alcohol consumption. *Aust New Zeal J Publ Health*. 1998; 22:621–623.
102. Doll R. Smoking and dementia in male British doctors: prospective study. *BMJ*. 2000; 320:1097–1102. [PubMed: 10775216]
103. Juan D, Zhou DHD, Li J, Wang JYJ, Gao C, Chen M. A 2-year follow-up study of cigarette smoking and risk of dementia. *Eur J Neurol*. 2004; 11:277–282. [PubMed: 15061830]
104. Launer LJ, Andersen K, Dewey ME, Letenneur L, Ott A, Amaducci LA, Brayne C, Copeland JRM, Dartigues JF, Kragh-Sorensen P. Rates and risk factors for dementia and Alzheimer's disease: results from EURODEM pooled analyses. *Neurology*. 1999; 52:78–84. [PubMed: 9921852]
105. Laurin D, Masaki KH, Foley DJ, White LR, Launer LJ. Midlife dietary intake of antioxidants and risk of late-life incident dementia: the Honolulu-Asia Aging Study. *Am J Epidemiol*. 2004; 159:959–967. [PubMed: 15128608]
106. Luchsinger JA, Reitz C, Honig LS, Tang MX, Shea S, Mayeux R. Aggregation of vascular risk factors and risk of incident Alzheimer disease. *Neurology*. 2005; 65:545–551. [PubMed: 16116114]
107. Merchant C, Tang MX, Albert S, Manly J, Stern Y, Mayeux R. The influence of smoking on the risk of Alzheimer's disease. *Neurology*. 1999; 52:1408–1412. [PubMed: 10227626]
108. Moffat SD, Zonderman AB, Metter EJ, Kawas C, Blackman MR, Harman SM, Resnick SM. Free testosterone and risk for Alzheimer disease in older men. *Neurology*. 2004; 62:188–193. [PubMed: 14745052]
109. Piguet O, Grayson DA, Creasey H, Bennett HP, Brooks WS, Waite LM, Broe GA. Vascular Risk Factors, Cognition and Dementia Incidence over 6 Years in the Sydney Older Persons Study. *Neuroepidemiology*. 2003; 22:165–171. [PubMed: 12711848]
110. Yoshitake T. Incidence and risk factors of vascular dementia and Alzheimer's disease in a defined elderly Japanese population: the Hisayama Study. *Neurology*. 1995; 45:1161–1168. [PubMed: 7783883]
111. Hebert LE, Scherr PA, Beckett LA, Funkenstein HH, Albert MS, Chown MJ, Evans DA. Relation of Smoking and Alcohol Consumption to Incident Alzheimer's Disease. *Am J Epidemiol*. 1992; 135:347–355. [PubMed: 1550089]
112. Katzman R, Aronson M, Fuld P, Kawas C, Brown T, Morgenstern H, Frishman W, Gidez L, Eder H, Ooi WL. Development of dementing illnesses in an 80-yearold volunteer cohort. *Ann Neurol*. 1989; 25:317–324. [PubMed: 2712531]
113. Smith, CJ.; RJR. Conversation with Dr. Robert Katzman. RJ Reynolds: 1987 May 25 [27 May 1987]. (870525). <http://legacy.library.ucsf.edu/tid/sxu63d00>
114. Stone, D. Council for Tobacco Research. [29 Dec 1986]. Grant Application #2134 J. G. Joshi, Ph.D. <http://legacy.library.ucsf.edu/tid/atr00d00>
115. Stone, D. Council for Tobacco Research. [02 Feb 1987]. Grant Application #2134 J.D. Joshi, Ph.D. <http://legacy.library.ucsf.edu/tid/xsr00d00>
116. Smith, C.; Simmons, S. Smoking and Health DIV. Nicotine and Alzheimer's Disease. RJ Reynolds: [07 Oct 1987]. Rdm87 1. <http://legacy.library.ucsf.edu/tid/les03a00>
117. Funding Levels. RJ Reynolds: 1992 [02 Aug 1991]. Extramural Nicotine Research Proposed. (920000) <http://legacy.library.ucsf.edu/tid/ifz53d00>

118. Smoking & Health Contract Research Program. RJ Reynolds: 00 1989.
<http://legacy.library.ucsf.edu/tid/fnf97c00>
119. Consultancy - PN Lee. Philip Morris: [00 Oct 1993]. <http://legacy.library.ucsf.edu/tid/sej14e00>
120. Lee, PN. Current and Recent Activities. Philip Morris: [13 Oct 1994].
<http://legacy.library.ucsf.edu/tid/tlx85e00>

Figure 1.
Random effects meta-analysis of studies of AD.

Figure 2.

A funnel plot shows no evidence of publication bias among all the studies (Begg's Test $P=.97$). We also did a similar analysis for the four different subsets of studies (case-control, no tobacco affiliation, $P=.544$ by Begg's test; case-control, tobacco affiliated, $P=.476$; cohort, no tobacco affiliation, $P=.536$; cohort, tobacco affiliation, $P=.999$), which also failed to find evidence of publication bias.

Case-control studies investigating the association between smoking and Alzheimer’s disease

Table 1

No tobacco industry affiliation											
Author, year	# of cases /#who smoked	# of controls/#who smoked	OR	95%CI	Estimates Adjusted for	Source of Cases	Source of Controls	Smoking Exposure Measure	Outcome Measure/ Diagnosis of AD	Tobacco Industry Affiliation	Industry Affiliation Disclosed in Published Article***
Amaducci et al., 1986[65]	51/116	52/97	1.83	0.62–6.04	Age, sex, region of residence	Dept of Neurology	Hospital or community acquaintance	Ever smoked ≥ 10 cig/day Never	Clinical assessment and Blessed Dementia Scale	None	
Brenner et al., 1993[66]	152/?	180/?	0.61	0.37–0.99	Age, gender, education, race, hypertension	AD registry	Same population as cases	Ever/Never	NINCDS-ADRD	None	
Broe et al., 1990[67]	170/80	170/88	0.76	0.44–1.31	Age, gender, general practice of origin	Dementia clinics	Same referring practice	Ever ≥ 1 pk cigs/day Never	NINCDS-ADRD	None	
Chandra et al., 1987[68]	62/16	62/22	0.57	0.21–1.46	Age, race, gender, agents, education, occupation	Seniors out patient clinic	Non-demented same clinic	Unclear	NINCDS-ADRD	None	
Debanne et al., 2000[69]**	86/49	152/78	1.26	0.66–2.42		Research Registry at AD Center	siblings	Ever/Never	Blessed Dementia Scale	Not for this work**	
Ferini-Strambi et al., 1990[70]	63/16	126/53	0.47	0.24–0.91	Age, gender, residential area, education, social status, age of onset	Department Neurology	Case neighbors	Ever ≥ 10cig/day after the age of 30 Never	NINCDS-ADRD	None	
Forster et al., 1995[71]	109/66	109/77	0.65	0.35–1.17	Age, gender, atherosclerotic disease	Referrals to specialist hospital services	Random from same population	Ever/Never	NINCDS-ADRD	None	
French et al., 1985[72]	78/54	48/37	0.50	0.15–1.66	Age, race, gender	VA hospital	Hospital and neighborhood	Unclear	Insidious onset, gradual progression of dementia intact LOC	None	
Harwood et al., 1998[46]white non-Hispanic	392/58	202/59	1.10	0.70–1.60	Age, gender, education, ethnicity	AD center	Non-demented from same center	Ever/Never	NINCDS-ADRD	None	
Harwood et al., 1998[46]white Hispanic	188/30	84/36	1.00	0.50–1.90	Age, gender, education, ethnicity	AD center	Non-demented from same center	Ever/Never	NINCDS-ADRD	None	
Heyman et al., 1984[73]	12/40	25/80	0.94	0.40–2.13	Age, gender, race	Epidemiology study database	Telephone sample	Ever ≥ 1pk/day after 40 yo Never	unclear	None	
Maia et al., 2002[74]	54/?	54/?	1.41	0.59–3.33	Age, Gender, monozygotic/dizygotic	Dementia Outpatient Clinic	Accompanied patient	Never, Past, Current	NINCDS-ADRD	None	
Prince et al., 1994[75]	19/4	118/13	2.15	0.66–7.17	Age, gender, hypertension	Study of hypertension	Same population	Current smoking Never	NINCDS-ADRD	None	
Salib et al., 1997[38]	198/72	176/72	0.83	0.54–1.25	Age, gender, age of onset, duration of condition, history of head injury, and family history of dementia	Geriatric practice	Non-demented referrals	Ever/Never	NINCDS-ADRD	None	

No tobacco industry affiliation											
Author, year	# of cases /#who smoked	# of controls/ #who smoked	OR	95%CI	Estimates Adjusted for	Source of Cases	Source of Controls	Smoking Exposure Measure	Outcome Measure/ Diagnosis of AD	Tobacco Industry Affiliation	Industry Affiliation Disclosed in Published Article ^{****}
Shaji et al., 1996[76]	27/3	34/4	0.94	0.21–4.16	Age, gender, education	Community survey in India	Same population	Unclear	ICD-10	None	
Shalat et al., 1987[77]	98	162	1.53	0.74–3.17	Gender, year of birth, town of residence, severe head trauma, alcohol consumption, education	Research Center	Neighbors	Ever/Never	NINCDS-ADRDA	None	
van Duijn et al., 1991[78]	193/89	195/102	0.70	0.43–1.15	Age, gender, abnormalities on computed tomography, focal dysfunction on electroencephalography	Community	Community	Ever/Never	NINCDS-ADRDA	None	
Wang et al., 1997[79]	98/45	97/26	1.73	0.8–2.66	Age, gender, computerized tomography for vascular or other structural lesions.	Clinic	Spouses	Daily current or past/ Never	NINCDS-ADRDA	None	
Pooled^{****}			0.91	0.75–1.10							

Tobacco Industry Affiliation											
	285/97	158/54	1.00	0.69–1.50	Age, race, education, alcohol exposure, head trauma, APOE-4	African Americans in the MIRAGE study	Siblings	Ever /Never	NINCDS-ADRDA	Friedland team “participated with” [80] MIRAGE study group, shared data and co-authored on acknowledged tobacco funding publications [81,82]	No
Bachman et al., 2003[45]African American											
Bachman et al., 2003[45]White	1,650/834	686/374	0.88	0.73–1.10	Age, race, education, alcohol exposure, head trauma, APOE-4	Whites in the MIRAGE study	Siblings	Ever/Never	NINCDS-ADRDA	Friedland team “participated with” [80] MIRAGE study group, shared data and co-authored on acknowledged tobacco funding publications [81,82]	No
Barclay et al., 1989[83]	14/39	12/39	1.26	0.50–3.20	Age, gender, alcohol habits	Hospital notes	Spouses	Ever/Never	NIH criteria and Absence of symptoms compatible with vascular dementia	Funded by CTR 1985–1987[23,83–85]	Yes
Bowirrat et al., 2001[35]	168/30	na*	0.70	0.40–1.30	Age, gender, education	Survey of Israeli community	Same population as cases	Yes is current or stopped ≥ 1 year ago or No	DSM-IV	Co-PI with Friedland at Tel Aviv University site, funded by PM[86] [87]	No
Graves et al., 1990[88]	130/67	130/76	0.88	0.67–1.15	Age	2 clinics	Friend or surrogate	Ever (1 year prior to illness)	NINCDS-ADRDA	Co-PI with Friedland, funded by PM[89,90]	No
Lemer et al., 1997[91]	88/?	176/?	0.89	0.42–1.36	Age, gender, estrogen replacement	Unclear	Unclear	Unclear	NINCDS-ADRDA	Co-PI with Friedland, funded by PM [89,90,92,93]	Yes
Plassman et al., 1995[94]	65/?	65/?	0.66	0.33–1.35		Twins	Twin discordant for AD	Ever (20 pack yr life time history)	NINCDS-ADRDA	Levin, Breitner, Welsh team funded by RJR [95–98]	Yes
Wang et al, 1999[47]	106/24	438/138	0.60	0.40–1.10	Age, sex, education	Community	Community	Ever	DSM – III-R	Senior author Winblad, history of funding by Swedish Tobacco Co [99]	No

Tobacco Industry Affiliation									
Pooled	****						0.86	0.75-0.98	

? unknown number of smokers

* Prevalence study

** Debanne is considered not tobacco industry affiliated for this study because the this work was done without Tobacco Industry affiliation. PM initially funded Debanne as Co-PI with Friedland, for a pilot study, but PM refused to continue to fund “siblingsstudy” reported here.

*** Entries only for authors with industry affiliations

**** Q test for heterogeneity = 23.66, DF = 17, P = .129.

***** Q test for heterogeneity = 4.28, DF = 7, P = .748.

Cohort Studies Investigating The Association Between Smoking And Alzheimer’s Disease

Table 2

No Tobacco Industry Affiliation											
Study	Cohort, <i>n</i>	Incident cases of AD with info about smoking	RR	95%CI	Estimates adjusted for	Source of Cohort	Duration of Follow-up	Smoking Exposure Measure	Outcome Measure/ Diagnosis of AD	Tobacco industry affiliation	Industry Affiliation Disclosed in Published Article*
Aggarwal et al., 2006[100]	1,064	170	3.40	1.40–8.00	Age, gender, race, APOE-4	Chicago IL Community	4.1 years	Current	NINCDS-ADRD	None	
Broe, et al., 1998[101]	327	31	1.03	0.45–2.37	Age (at follow-up) gender, education	Community department of VA	3 years	Current, Former, Never	NINCDS-ADRD	None	
Doll et al., 2000[102]	24,133	370	0.99	0.78–1.25	Age, gender	Male British Doctors	1950–death	Never, Ever, Continuing	NINCDS-ADRD	None	
Hirayama et al., 1992[51]	265,118	120	1.61	1.10–2.38	Age, gender	Japanese Community	Up to 27 years (until death)	Daily, Occasionally, Former, Never	NINCDS-ADRD	None	
Juan et al., 2004[103]	2,820	84	2.72	1.63–5.42	Age, sex, education, BP, and alcohol intake	Chinese Community	2 years	Never and Current	MMSE and DSM-III-R	None	
Launer et al., 1999[104]	10,889	145	1.74	1.00–2.40	Age, age squared, study, sex, and education	EURODERM Eastern Europe community	5-year bands	Ever	NINCDS-ADRD	None	
Laurin et al., 2004[105]	2,341	134	1.55	1.00– 2.40	Age, education, alcohol intake, body mass index, physical activity, blood pressure, year of birth total energy intake, cholesterol concentration, history of CVD, supplemental vitamin intake, APOE-4, and Vitamin E	Hawaiian community, Japanese American Men	Varied, up to 2 times over 8 years	Never, Past, and Current	DSM-III; NINCDS-ADRD	None	
Lindsay et al., 2002[41]	3,973	182	0.82	0.57–1.17	Age, sex, education	Canadian Study of Health and Aging	5 years	Ever	NINCDS-ARDA	None	
Luchsinger et al., 2005[106]	1,012	61	2.0	1.3–3.2	Age, sex, education, APOE-4, diabetes, hypertension, and heart disease	North Manhattan community	1.5 years	Current, Never	NINCDS-ADRD	None	
Merchant et al., 1999[107]	1,204	142	1.90	1.20–3.0	Education, ethnicity	Medicare recipients in 3 contiguous zip codes	Varied mean 1.7 years	Current, Former, Never	DSM-IVNINDS-ADRD	None	
Moffat et al., 2004[108]	572	54	1.86	1.39–2.49	Age, education, BMI, diabetes, cancer, hormone supplementation, and free testosterone index	Baltimore Longitudinal Study of Aging	Varied 4-37 years; mean 19.1 years	Ever	DSM-III-RNINDS-ADRD	None	
Pignat, et al., 2003[109]	377	21	0.51	0.21–1.21	Age at entry	Sydney Australia	6 years	Smoking Nonsmoking	NINCDS-ADRD	None	
Reitz, et al., 2007 [39]	6,868	555	1.51	1.0–2.08	Age, gender, APOE-4, education, alcohol intake	The Rotterdam Study	7.1 years	Never, Past, Current	NINCDS-ADRD	None	

No Tobacco Industry Affiliation											
Study	Cohort, <i>n</i>	Incident cases of AD with info about smoking	RR	95%CI	Estimates adjusted for	Source of Cohort	Duration of Follow-up	Smoking Exposure Measure	Outcome Measure/ Diagnosis of AD	Tobacco industry affiliation	Industry Affiliation Disclosed in Published Article [*]
Yoshihake et al., 1995[110]	828	42	0.73	0.5–2.4	Age, gender	Hisayama, Japan	7 years	Ever, Never	NINCDS-ADRDA	None	
Pooled^{**}			1.45	1.16–1.80							

Tobacco Industry Affiliation											
Hebert et al., 1992[111]	513	76	0.70	0.30–1.40	Age, gender, education	Boston MA Community	4.7 years	Ever	NINCDS-ADRDA	Worked with PN Lee and Paid consultant for PM[52,54]	No
Katzman et al., 1989[112]	434	32	0.27	0.11–0.61	Age, gender	Bronx NY Volunteers	unclear	Current or Past	NINCDS-ADRDA	Paid consultant for CTR[113–115]	No
Wang et al., 1999[47]	343	34	1.1	0.5–2.4	Age, sex, education	Stockholm, Sweden	3 years	Ever, Never	DSM-III-R	Senior author Winblad, history of funding by Swedish Tobacco Co [99]	No
Pooled***			0.60	0.27–1.32							

* Entries only for authors with industry affiliations

** Q test for heterogeneity = 43.34, DF = 13, P < .0005.

*** Q test for heterogeneity = 5.77, DF = 2, P = .056.

Table 3

Multivariate determinants of AD risk

Factor	Coefficient	SE	t	P	VIF
Case-control study design	-.27	.15	-1.83	.075	1.39
Journal Impact Factor*	-.002	.009	-0.22	.828	1.16
Year (2007 = 0)	.031	.013	2.43	.020	1.30
Tobacco Affiliation	-.37	.13	-2.80	.008	1.24
Constant**	1.72	.19	8.84	<.0005	

N=43; $R^2 = 0.334$; $P = .006$ for overall regression. Weights are sampling weights from random effects meta-analysis (Stata pweights).

* Centered on mean value of 6.343

** The constant is an estimate of the risk estimate based on a cohort study published in a journal with the average impact factor in 2007 by authors not affiliated with the tobacco industry.

Table 4

Reviews Of Smoking And Alzheimer's Disease Reviews And Tobacco

Author and Date	Conclusion	Protective Effect	Tobacco industry Affiliation
Graves, A.B., van Duijn, C.M., et al., 1991[10]	"A statistically significant inverse association between smoking and Alzheimer's disease was observed at all levels of analysis, with a trend towards decreasing risk with increasing consumption."	Yes	Graves was a co-PI with Friedland funded by PM[89,90]
Smith, C.J. & Giacobini, E. 1992[12]	"...nicotine or nicotine-like compounds may be useful in the amelioration of the attention and memory deficits associated with AD."	Yes	Smith was employed by RJR [116] and Giacobini funded by RJR[117,118]
Van Duijn, C.M., et al., 1994[13]	"... the odds ratio associated with family history of dementia tended to be lower for those with a positive smoking history..."	Yes	Graves[89,90] co-PI with Friedland, funded by PM and Fratiglioni[99] co-PI with Winblad, funded by Swedish Tobacco Co.
Lee, P.N., 1994[11]	"... the negative association is consistent with other data suggesting nicotine protects against AD."	Yes	Lee was a long term statistical consultant for the tobacco industry. [117,119,120]
Fratiglioni, L. & Wang, H., 2000[9]	"...a negative association for AD is controversial...not a clear effect"	Ambiguous	No *
Turner, C. & Spilich, G.J., 1997[18]	" Scientists acknowledging tobacco industry support reported typically that nicotine or smoking improved cognitive performance while researchers not reporting the financial support of the tobacco industry were more nearly split on their conclusions."	Ambiguous	No
Almeida, O.P., et al., 2001[5]	"Case-control and cohort studies produce conflicting results as to the direction of the association between smoking and AD."	Ambiguous	No
Anstey, K.A., et al., 2007[6]	"elderly smokers have increased risks of dementia and cognitive decline".	No	No
Hernan, M.A., et al., 2008[7]	"...selection bias due to censoring by death may be the main explanation for the reversal of the relative rate with increasing age."	No	No
Purnell, C., et al., 2008[8]	"...four separate studies reported on the effect of smoking on incident AD. Three studies...reported that current smoking increased the risk of incident AD...an additional article...recorded only smoking and found that it was not significant."	No	No

* Fratiglioni and Wang were research associates with Winblad, funded by Swedish Tobacco Co. 15 years earlier,[99] which we considered long enough ago to consider no Tobacco Affiliation for this review.