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Smoking history and Alzheimer's disease risk in a community-based clinic population

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Abstract:

BACKGROUND: The relationship between cigarette smoking and development of Alzheimer's disease (AD) is not fully determined, and previous reports disagree, with some studies suggesting an increased relative risk and others a decreased odds ratio. Consequently, we wanted to determine if the prevalence of past cigarette smoking observed in a community-based clinic sample of patients with AD would be more consistent with the expected value obtained from a model using either an increased relative risk or a decreased odds ratio to estimate the effect of smoking on development of AD.

MATERIALS AND METHODS: Retrospective cross-sectional analysis of all patients treated for AD in a community-based Neurology Clinic during a 2-year period. Estimates of expected past smoking prevalence were calculated based on published values for either an increased relative risk or a decreased odds ratio and compared to the past smoking prevalence observed in the clinic sample.

RESULTS: The observed past smoking prevalence in the clinic population was 29.17%. The expected past smoking prevalence calculated using the increased relative risk was 30.07% (95% confidence interval [CI] = 27.67–32.32%), and using the decreased odds ratio was 12.54% (95% CI = 6.32–24.81%).

CONCLUSION: The observed past smoking prevalence among the patients being treated for AD in a community-based clinic falls within the expected 95% CI for the increased relative risk model and outside of the expected 95% CI for the decreased odds ratio model. These results support the contention that the relationship between cigarette smoking and development of AD is the best characterized by an increased relative risk.

Keywords:

Alzheimer's disease, dementia, epidemiology, smoking

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Introduction

The American Alzheimer's Association estimates that approximately 5.2 million Americans currently suffer from Alzheimer's disease (AD),[1,2] and that the prevalence of AD, as well as other dementias, will continue to grow and may affect up to 16 million individuals by 2050.[1,2] The importance of this public health concern is further illustrated by estimates of the direct costs associated with caring for individuals with AD which some have suggested may be as high as $214 billion/year and may increase to almost $1.2 trillion dollars by 2050.[1-3]

As the number of people affected by this disorder and the costs for caring for them increase, it will also be increasingly important to identify behavioral risk factors that can be altered to reduce risk for developing the disease and thereby decrease the societal burden of this disorder. Unfortunately, previous reports disagree regarding the relationship between cigarette smoking and development of AD, with some reporting an increased relative risk and others reporting a decreased odds ratio.[4] For example, a recent meta-analysis by Cataldo *et al*. in 2010, identified 43 prospective studies examining the relative risk for development of AD associated with smoking.[4] After controlling for study design, quality, and tobacco industry affiliation of the

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authors, they found a significant relationship between funding source and study outcome.[4] They concluded the results of eight case _control studies with tobacco industry affiliation resulted in a decreased odds ratio for developing AD associated with cigarette smoking, while the pooled relative risk obtained from 14 cohort studies without tobacco industry affiliation indicated the opposite relationship with an increased relative risk for developing AD associated with cigarette smoking.[4] The authors concluded that study design influenced results with case _control studies resulting in lower average risk estimates than cohort studies; and that industry sponsorship also influenced results of studies, with industry-sponsored studies being more likely to report a decreased relative risk for development of AD associated with cigarette smoking.[4]

Because previous studies do not agree if the relationship between cigarette smoking and development of AD is better characterized as an increased relative risk or a decreased odds ratio, and due to the report of potential bias from industry sponsorship of some past studies, it is important to re-examine the question using data from an unbiased source such as a community clinic population. Consequently, the objective of our study was to determine, if the prevalence of current and past smoking observed in a cohort comprised all AD patients seen in a community-based clinic would be more consistent the predicted value calculated using either an increased relative risk or a decreased odds ratio to characterize the relationship between cigarette smoking and development of AD. We chose to use the pooled risk estimates from the study by Cataldo *et al*., for estimates of both the increased relative risk and the decreased odds ratio that have previously been identified.[4] We hypothesized that the rates of current and past cigarette smoking observed among the AD patients in our sample would be more consistent with the estimated value obtained using an increased relative risk than using a decreased odds ratio.

Materials and Methods

Participants

Participants were adults, over the age of 18 years, who presented sequentially to a community-based Neurology Clinic located in Torrance, California, USA during a 2-year period from January 1, 2012 to December 30, 2013 for treatment of AD. De-identified data were obtained from our Neurology Department database for all patients seen in the clinic during the study period and diagnosed with dementia according to International Classification of Diseases-9 code. Past smoking status was obtained from the database and was coded as either positive or negative. Local Institutional Review Board approval was obtained for retrospective analysis of de-identified database data as part of our ongoing Neurology Department database project. Informed consent was waived since the project consisted of a retrospective analysis of already acquired de-identified clinical data.

Study design

A retrospective cross-sectional study design was used to obtain the observed prevalence of past smoking among the patients with AD treated in the clinic during the study period.

Statistical analysis and calculations

The observed past smoking prevalence value was calculated using the formula: OPcs = Nps/(Nns + Nps); where OPcs = the observed prevalence of cigarette smokers in the clinic, Nps = the number of past smokers seen in the clinic, and Nns = the number of nonsmokers seen in the clinic.

Expected past smoking prevalence values were calculated for each of two different scenarios: one using an increased relative risk for development of AD associated with smoking of 1.72 (95% confidence interval [CI]: 1.53–1.91) as the risk estimate;[4] and one using the decreased odds ratio of 0.60 (95% CI: 0.27–1.32) as the risk estimate.[4] The expected prevalence of cigarette smoking was calculated according to the formula: $EP_{CS} = EN_{CS}/(EN_{NS} + EN_{CS})$; where EP_{CS} is the expected prevalence of cigarette smokers, EN_{CS} is the expected number of cigarette smokers, and EN_{NS} is the expected number of nonsmokers. The expected number of cigarette smokers was calculated according to the formula: $EN_{CS} = N\ (R_S)\ (R_{AD})\ (RF)$; where EN_{CS} is the expected number of cigarette smokers, N is a constant used to denote a larger number of the general population from which the sample is derived, R_S = the rate of cigarette smoking in the general population,[5] R_{AD} = the published population risk for developing AD,[6] and RF = the risk factor applied to the risk of developing AD which is equal to either the relative risk or odds ratio for developing AD associated with cigarette smoking depending on the scenario being calculated.[4] The expected number of nonsmokers was calculated according to the formula: $EN_{NS} = N\ (1\text{-}R_S)\ (R_{AD})$; where EN_{NS} is the expected number of nonsmokers, N is a constant used to denote a larger number of the general population from which the sample is derived, R_S = the rate of cigarette smoking in the general population,[5] and R_{AD} is the published population risk for developing AD.[6]

The expected past smoking prevalence values calculated for each scenario were then compared to the observed smoking prevalence observed in our clinic population. Mean values for continuous demographic factors and other continuous variables were compared between groups using two-tailed *t*-tests. Nonparametric data were compared between groups using either the Chi-square test or Fisher's exact test as appropriate. All statistical calculations were performed using SPSS version 22, (IBM Corp.: Armonk, NY).[7]

Results

A total of 123 patients were evaluated for dementia in the clinic during the study period. Of those, 48 were excluded from the study because they were being

evaluated or treated for disorders other than AD. An additional three patients were excluded because they did not have documented smoking histories. A total of 72 patients were included in the study, including 21 with positive past cigarette smoking histories and 51 with negative past smoking histories.

Overall, the groups showed similar demographics and did not differ significantly in the frequency of potentially confounding factors such as mean age or mean dementia onset age [Table 1]. The groups also did not differ significantly in the frequency of other potential confounders such as the use of alcohol or illicit substances, or in the presence of psychiatric symptoms [Table 1]. However, the groups did differ significantly in gender distribution (P = 0.034), with greater frequency of male gender present in the positive past smoking group [Table 1].

The expected past smoking prevalence for the increased relative risk scenario was calculated to be 30.07% (95% CI: 27.67–32.32%) [Figure 1]. The expected past smoking prevalence for the decreased odds ratio scenario was calculated to be 12.54% (95% CI: 6.32–24.81%) [Figure 1]. The observed past smoking prevalence among our AD population was 29.17% (21/72), which falls within the 95% CI for the increased relative risk scenario, but outside of the 95% CI for the decreased odds ratio scenario [Figure 1]. Additionally, we calculated the smoking rate in the general population that would be needed to achieve the past smoking prevalence observed in our AD population under the decreased odds ratio scenario. To achieve the observed past smoking prevalence of 29.17% observed in our AD population using the decreased odds ratio scenario would require a smoking rate of 54.91% in the general population with a 95% CI of 24.96–122.00%.

Discussion

The results of this study support the relationship between cigarette smoking and development of AD being best characterized as an increased relative risk. Additionally, the results of this study serve to highlight the potential dangers of industry sponsorship of scientific studies which may introduce nonobvious sources of bias that can influence results and conclusions. Consequently, we feel that it is important to continue to support work that uses data obtained from populations of "real world" or clinical samples, which are more likely to be free of potential sources of bias and therefore can be used as a means to check the validity of results of sponsored studies or studies that rely on data obtained from populations of patients that are created purely for research purposes.

The potential for industry sponsorship to introduce bias into clinical studies is shown by a recent study by Cataldo *et al*., in which they identified three previous studies in particular which acknowledged Tobacco industry sponsorship and concluded that cigarette smoking was associated with decreased risk for development of AD or protected against development of AD.[4,8-10] Despite calling attention to this potential example of bias identified in a series of industry-sponsored studies, the issue of how cigarette smoking affected risk for development of dementia remained controversial and the subject of ongoing debate. The following year in 2011, Rusanen *et al*., continued the debate on this issue by reporting results from a population-based cohort study investigating the effects of smoking during mid-life on risk of developing dementia, AD, and vascular dementia later in life.[11] They concluded that heavy smoking in midlife was associated with a greater risk for developing dementia and more specifically both AD and vascular dementia.[11] The results of our study add further support to the link between smoking and increased relative risk for developing AD, and

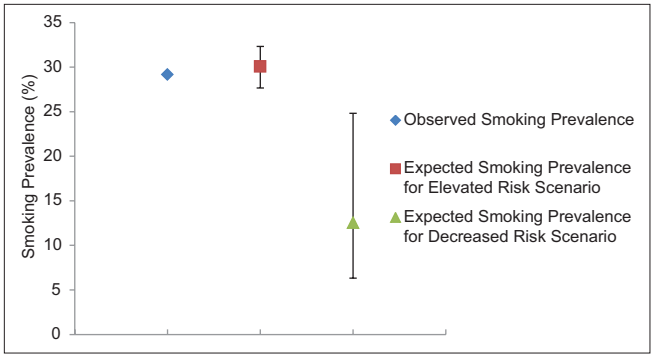

Figure 1: Observed smoking prevalence as compared to the expected smoking prevalence for an increased and decreased risk scenarios. Error bars denote 95% confidence interval limits

Table 1: Comparison of demographic factors between smokers and nonsmokers

Demographic characteristics	Smokers (n=21)	Nonsmokers (n=51)	Significant P
Mean age in years	65.26 (SD=11.65)	66.24 (SD=11.82)	0.759
Mean onset age in years	55.64 (SD=11.18)	62.09 (SD=12.09)	0.123
Female gender (%)	7 (33.33)	33 (64.71)	0.034
Alcohol use (%)	5 (23.81)	3 (5.88)	0.218
Illicit substance use (%)	1 (4.76)	0 (0.00)	0.415
Anxiety (%)	2 (9.52)	9 (17.65)	0.694
Depression (%)	6 (28.57)	19 (37.25)	0.789
Psychosis (%)	2 (9.52)	6 (11.76)	0.802

SD = Standard deviation

also demonstrate how data obtained from a clinical or population-based sample can be used to test if results of industry sponsored studies are supported by real world observations.

This study has several limitations. First, the retrospective nature of the study does not allow for assessment of causality. Also, self-report of past cigarette smoking may have resulted in underestimation of the past smoking prevalence in the clinic sample. Additionally, past cigarette smoking was treated as a positive or negative variable and not quantitated in terms of pack-years or other method, and other forms of tobacco or nicotine use such as cigars, electronic cigarettes, nicotine gum, and others were not assessed. The study also did not control for potential confounding factors including the possible effects of secondhand smoke which has itself been associated with both cognitive impairment and an elevated risk for developing dementia.[12,13]

Overall, the record in the scientific literature contains conflicting reports on the relationship between cigarette smoking and development of AD.[4] At least one previous study has suggested that evidence of bias related to funding source exists among published studies investigating this question.[4] The results of our study show that easily obtainable data from real world clinic populations can be used to help differentiate between opposing viewpoints when conflicting results of past studies exist. In this particular case, our results provide additional support for the contention that cigarette smoking is associated with an increased relative risk for development of AD and do not support the existence of any protective effect associated with cigarette smoking for reducing risk of developing AD.

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Conflicts of interest
There are no conflicts of interest

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