

# Effect of alcohol and tobacco use on vascular dementia: a matched case control study

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**Background:** Vascular dementia is the second most common type of dementia in the United States. The underlying association of tobacco and alcohol with vascular dementia is not completely understood.

**Purpose:** Determine the relationship of tobacco and alcohol use with the development of vascular dementia (VaD).

**Methods:** This was a matched case-control study of subjects living in Olmsted County, MN. Cases of VaD were identified through medical record abstraction using conventionally accepted definitions of VaD, using the National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIRENS) criteria and were matched to controls by gender and age within 3 years among persons free of dementia on the index date. Exposure data for alcohol and tobacco use were abstracted by trained nurses, along with demographic, lifestyle, cerebrovascular, cardiovascular, and vascular comorbid disease characteristics. Matched conditional logistic regression for univariate and multivariate evaluation of the association of tobacco and alcohol use with VaD was utilized.

**Results:** Current alcohol exposure was associated with a decreased risk of VaD with an odds ratio of 0.48 (95% confidence interval: 0.31–0.74). This protective effect of alcohol was seen in men, women, and subjects under 80 years of age. Tobacco use was not associated with VaD in univariate and multivariate analysis, and stratified analysis did not reveal any subgroup-specific associations between tobacco use and VaD in the study population.

**Conclusion:** Current alcohol use appears to have protective effects against the development of vascular dementia. The effects are more pronounced in subjects under age 80. This may reflect the direct vascular effects of alcohol on the vascular system or may represent a surrogate for better social or functional status. Previous alcohol use was not protective. Tobacco use was not a risk factor for VaD status, which was possibly an indication of survivorship bias in the cohort.

**Keywords:** vascular dementia, elderly, alcohol, tobacco

## Introduction

Vascular dementia (VaD) is a common and increasingly recognized illness that has some identifiable lifestyle comorbid risk factors. VaD involves cognitive decline with underlying pathological lesions of vascular ischemia or occlusion.<sup>1</sup> In a Midwestern autopsy study, VaD represented the second most common form of dementia, following Alzheimer's disease, and may account for up to 25% of dementia in the United States.<sup>2</sup> Internationally, there are differences in VaD prevalence. The Japanese suffer a higher prevalence of VaD than Americans,<sup>3</sup> perhaps demonstrating a cultural or ethnic component to the illness. The importance of lifestyle issues in these cultural

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differences remains incompletely characterized. Many of the lifestyle risk factors for vascular dementia have treatable components or may be protective. Thus, there is a need to understand how lifestyle issues, like tobacco and alcohol use, influence the development of vascular dementia.

Despite partial understanding of some of the risk factors for stroke, many questions remain about potential risk factors for VaD. One cannot assume that the risk factors for stroke and VaD are the same. The objective of this study was to determine the differences in risk from lifestyle exposures between individuals with VaD and controls without VaD. We evaluated the exposure to tobacco and alcohol in both VaD cases and in the control group. We hypothesized that tobacco use was a risk factor, as it is a risk factor for other vascular illnesses.<sup>4</sup> We further hypothesized that alcohol was protective against dementia.<sup>5</sup> To answer these questions, we undertook a matched case-control study in patients with well-documented VaD compared to age-matched controls.

## Method

### Study design

This study utilizes a retrospective, matched case-control analysis of patients living within Olmsted County, MN. The Mayo Clinic medical record system has over 70 years of medical records data from over 6 million patients and has been widely used for epidemiological studies.<sup>6</sup>

### Setting

The Mayo Clinic is the largest health care provider in Southeastern, MN, providing care at the primary, secondary, and tertiary levels. The time ranges included cases and controls from inpatient and outpatient medical care records from 1994–2002. Exposures were included for all times prior to determination of case or control status. All visits to Mayo Clinic providers are captured via physician notes, electronic medical records, and through clinical billing in an electronically integrated medical record system. These records are comprehensive and follow the patient throughout their life. Paper and electronic information sources were available and complete for all patients seen during the time of study initiation.

### Study subjects

#### Population

The US Census estimated Olmsted County's population to be 124,277 in 2000.<sup>7</sup> Educationally, 38.9% had a bachelor's degree or higher compared to 27.4% in the US at large. Of the Olmsted County population, 90.3% were white, 4.3% Asian and 2.7% black or African American.<sup>7</sup>

### Cases

Cases were defined as patients with a clinically documented diagnosis of vascular dementia. Records were screened for any one of 40 diagnoses suggestive of dementia. The incident cases of VaD were drawn from these records. The diagnostic information to make the determination was obtained from medical histories, neuroimaging studies, and clinical diagnoses. The diagnosis of dementia was based on the National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria for VaD.<sup>8</sup> The date of diagnosis of VaD for the case represented the index date for each case-control pair. If a control developed dementia during the time frame of the study, after having been selected as a control, he or she was included as a case with a uniquely matched control. Status as a previous control was retained relative to that individual's matched case.

### Controls

Controls were dementia-free in the medical records with the corresponding case index data and were matched 1:1 for age ( $\pm 2$  years), gender, and Mayo Clinic registration number. Matching for registration number allowed for similar access times to the medical system.

### Exclusion criteria

Individuals with any diagnosis of dementia before 1994 were excluded from the study. Patients who refused authorization for medical records review were also excluded.

### Exposure variables

The lifestyle exposure variables were tobacco and alcohol use. We used a dichotomous representation of ever (yes/no), previous (yes/no), and current (yes/no) for tobacco use. The specific types of tobacco use were as described: cigarette use, cigar use, pipe, and chew/smokeless tobacco use. The subjects also reported the number of years of tobacco use. Alcohol use had a dichotomous representation of ever (yes/no), previous (yes/no), and current (yes/no). The subjects self-reported the number of years of alcohol use. The amounts of alcohol or tobacco were also recorded. Specific types of alcohol included beer, wine, and hard liquor. All lifestyle information was based on self-report from the patient. Patient personal history obtained from the prior date closest to the index date was used.

The characteristics of the cohort were also collected. Comorbid medical illnesses were defined based upon clinical

diagnosis or by guidelines. Cerebrovascular disease was defined as medically diagnosed history of stroke and/or transient ischemic attacks (TIA). Stroke or TIA was defined as ever or never, prior to the index date. Myocardial infarction was evaluated clinically and was defined as ever or never, prior to the index date. Congestive heart failure, angina, and atrial fibrillation were defined as ever or never, prior to the index date. Hypertension was defined based upon JNC VII criteria of systolic blood pressure (SBP) greater than 140,<sup>9</sup> prior to the index date. The exposure used was the presence or absence of hypertension. Diabetes was diagnosed clinically and was defined as ever or never, prior to the index date. Educational years were determined based upon the last year of education.

## Data acquisition

The primary information abstracted included medical diagnoses and surgical information, which was coded using the International Classification of Disease adapted code for hospitals (H-ICDA). Alcohol and smoking information were collected using a self-reported questionnaire that patients completed prior to a medical evaluation. A trained nurse abstractor obtained and recorded the information on an electronic spreadsheet (Excel, v 2003; Microsoft Corp, Redmond, WA). The abstractor was blinded to the study hypothesis and was not involved with any analysis of data. Further information on the case and control exposures was obtained from the Mayo Clinic records-linkage system.

We attempted to reduce bias by blinding the data abstractors to the purpose of the study. The subjects reported alcohol and smoking use in a clinical setting; thus, there was potential for under-reporting its use. Recall bias would be minimized because the questionnaires asked about recent, as well as previous use. Despite these efforts, the effects of bias were likely present.

## Sample size

All available subjects who met the criteria within the time frame described were enrolled within the case-control study, because of the relatively uncommon nature of the case status (VaD). Two hundred and five matched pairs were included within the analysis.

## Data analysis

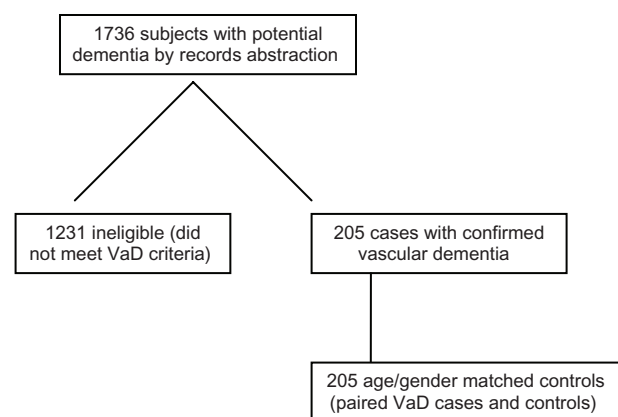
Simple descriptive statistics were calculated for demographic and exposure data among cases and controls, as well as for gender strata. The primary method of comparison between cases and controls utilized the odds ratio as a surrogate for

relative risk with 95% confidence intervals (95% CI). We utilized conditional logistic regression for analysis of the exposure variables between cases and controls. Subjects with missing information were excluded from analysis. We performed stratified conditional logistic regression for both gender and for age (<80 years and 80 years and above). All analyses were performed on Epi Info (v 3.5; Centers for Disease Control, Atlanta, GA).

## Results

In the study, 1736 potential subjects were identified using the initial evaluation from their medical records. From this group, the investigators identified 205 cases of VaD using standard criteria as noted above. The records of 1531 patients did not meet the criteria after medical record review. The schematic distribution is shown in Figure 1. The 205 pairs included 121 pairs of female subjects and 84 pairs of male subjects with an overall mean age of 81.9 years (SD: 7.79 years). The average length of educational involvement was 12.3 years (SD: 3.25 years). Comparing males and females, males had a lower age of 78.2 years (SD: 7.88 years) compared to 84.1 years (SD: 6.86 years) in females. The average educational achievement did not differ between the genders. The most common comorbid health condition was hypertension in the cohort, with 72.9% of cases and controls having hypertension. The full demographic and descriptive information of the overall cohort is noted in Table 1. Lifestyle exposures are listed in Table 2. These tables indicate the missing data. Missing data levels were high for specific alcohol type, and for the remainder of the variables between 8 and 17 were missing. The absolute numbers of exposures in cases and controls are listed.

Tobacco exposure (current, previous, ever) was not different between cases and controls in the univariate analysis



**Figure 1** Flow of subjects till final determination of cohort.

**Table 1** Demographic overview of cases of vascular dementia and controls in 205 matched pairs

	Overall (n = 410)	VaD cases (n = 205)	Controls (n = 205)
<b>Demographics</b>			
Male (%)	168 (41.0)	84 (41.0)	84 (41.0)
Age in years (SD)	81.9 (7.79)	82.1 (7.73)	81.6 (7.85)
Education in years (SD)	12.3 (3.25)	12.0 (3.35)	12.6 (3.13)
Body mass index, kg/m <sup>2</sup> (SD)	26.2 (5.02)	25.8 (4.50)	26.5 (5.40)
Obese, yes/no (%)	175 (53.4)	76 (51.4)	99 (55.0)
<b>History of comorbid health conditions</b>			
Stroke (%)	148 (37.0)	133 (65.8)	15 (7.6)
TIA (%)	80 (20.0)	66 (32.7)	14 (7.1)
CHF (%)	88 (21.8)	60 (29.3)	28 (14.1)
Angina (%)	130 (32.2)	70 (34.1)	60 (30.3)
Atrial fibrillation (%)	88 (21.8)	58 (28.3)	30 (15.1)
Previous MI (%)	78 (19.3)	41 (20.0)	37 (18.6)
Hypertension (%)	291 (72.9)	161 (80.1)	130 (65.7)
Diabetes (%)	101 (24.7)	64 (31.2)	37 (18.1)

**Abbreviations:** VaD, vascular dementia; TIA, transient ischemic attack; CHF, congestive heart failure; MI, myocardial infarction.

in the overall cohort. There also was no difference between different types of tobacco and VaD status. Lastly, there was no association between years of tobacco use and case or control status. These findings are noted in Table 3. We stratified the cohort by gender (male and female), and we did not find differences in tobacco exposure between cases and controls. Lastly, we stratified the analysis by age (under and over 80 years of age) and again did not find a difference in tobacco use (current, previous, ever). Tobacco frequency or amount of tobacco use also was not significantly different between VaD cases and controls.

Current alcohol use exposure was protective with an odds ratio of 0.48 (95% CI: 0.31–0.74). Previous alcohol use and ever alcohol use did not have a significant effect

**Table 2** Alcohol and tobacco exposure in a cohort of 410 subjects

Exposure	Cases	Controls	Missing data
<b>Alcohol use</b>			
Alcohol, current	53/199	86/198	13
Alcohol, previous	149/199	153/194	17
Alcohol, ever	149/199	154/195	16
Beer	56/167	59/166	77
Wine	48/167	54/166	77
Hard liquor	75/168	94/166	76
<b>Tobacco use</b>			
Tobacco, current	17/198	11/199	13
Tobacco, previous	112/201	111/201	8
Tobacco, ever	112/201	111/201	8
Cigar	7/201	8/199	10
Pipe	12/201	9/199	10
Chew/snuff	4/201	3/199	10

in the overall cohort. Specific alcohol type did not provide protection or serve as a risk in the overall cohort (Table 3). In the gender subgroup analysis, there was a similar protective effect of current alcohol use in both females, with an odds ratio of 0.45 (95% CI: 0.25–0.84), and males, with an odds ratio of 0.52 (95% CI: 0.28–0.96). The remaining types of alcohol use (previous or ever) were not significant in the gender subgroup analysis. The only additional significant value was a slight protective effect of wine use in women with an odds ratio of 0.52 (95% CI: 0.27–0.99). In the age subgroup analysis, current alcohol use did not achieve significance in adults under 80 years of age. It was significant in adults over 80 with an odds ratio of 0.31 (95% CI: 0.15–0.66). All remaining factors for alcohol use were not significantly different between the overall cohort and the age stratified cohort.

The duration of smoking or alcohol use did not show a difference between VaD cases and controls. The number of years of tobacco use was not associated with VaD status and was similar in both cases and controls. The number of years of alcohol use was also not associated with VaD between cases and controls. These findings were also found in the subgroup analysis by gender for both alcohol and tobacco use. Stratification by age did not provide additional information on different types of alcohol use or tobacco use.

## Discussion

Vascular dementia remains a growing public health issue as our society faces the demographic tsunami of an aging populace. In the US, the old (>65 years) and the oldest old (>80 years), will continue to expand into 2040, and stand as the fastest growing sections of the population.<sup>10</sup> The diagnosis of VaD remains somewhat challenging; however, the NINDS-AIREN criteria currently stand as the accepted standard for VaD diagnosis. Agreement among different providers using NINDS-AIREN criteria has been moderate to good.<sup>11</sup> In numerous longitudinal studies, increasing age has a strong association with increased prevalence of VaD.<sup>12,13</sup> In our study, we found that tobacco use did not contribute to an increased risk of VaD, while current alcohol use was protective.

## Tobacco use

We evaluated tobacco use by looking at current, previous, and ever use, while also looking for a dose effect. All of these risk variables were non-significant, with current use of tobacco having the highest but nonsignificant odds ratio of 1.67 (95% CI: 0.73–3.81). We evaluated tobacco use by

**Table 3** Univariate analysis of demographic and lifestyle risk factors for 205 matched pairs of vascular dementia cases and healthy controls

	Odds ratio	Lower 95% CI	Upper 95% CI	P value
Demographics				
Age	1.39	1.13	1.69	0.002*
Education in years (SD)	1.00	1.00	1.001	0.87
Lifestyle alcohol use				
Alcohol, current	0.48	0.31	0.74	0.001*
Alcohol, previous	0.80	0.49	1.31	0.38
Alcohol, ever	0.80	0.49	1.31	0.38
Beer, ever	0.88	0.50	1.55	0.67
Wine, ever	0.78	0.48	1.24	0.29
Hard liquor, ever	0.64	0.40	1.04	0.07
Number of years drinking	0.99	0.98	1.01	0.31
Tobacco use				
Tobacco, current	1.67	0.73	3.81	0.23
Tobacco, previous	1.00	0.66	1.52	1.00
Tobacco, ever	1.00	0.66	1.52	1.00
Cigar, ever	0.88	0.32	2.41	0.80
Pipe, ever	1.33	0.56	3.16	0.51
Chew/snuff, ever	1.00	0.20	4.95	1.00
Number of years smoking	1.01	1.00	1.02	0.12

**Note:** \*Reached statistical significance.

tobacco type and did not find an association between specific tobacco type and VaD status. Subgroup analysis did not show any significant association between tobacco use and VaD. However, there were some interesting trends that were noted. In the younger and female populations, there was no association between tobacco status and case status. Men who had previously or ever used tobacco seemed to have some trends toward higher odds ratios, but these trends did not reach significance. The older population (80+ years old) also seemed to have a trend toward a higher odds ratio of VaD. Our study population represents a primarily white population which differs from other studies. The novel findings in this study include a lack of associations with different age or gender subgroups and with different tobacco products. The lack of a consistent relationship between VaD and tobacco use may reflect survivorship bias in that patients who smoke and survived to develop VaD are different to those who died. The apparent protective effects of smoking in Alzheimer's disease and Parkinson disease have been attributed to survivorship bias.<sup>14</sup>

The results of previous studies on the effect of smoking and VaD have been mixed. Smoking stands as an important risk factor for stroke<sup>15</sup> and may be a potential risk factor for VaD. However, the direct evidence that smoking affects VaD has been unimpressive. A recent meta-analysis of the relationship between VaD and smoking had a nonsignificant odds ratio of 1.35 (95% CI: 0.90–2.02).<sup>16</sup> In a Chinese study of six communities, there was an association of VaD with

smoking with a relative risk of 1.98 (95% CI: 1.53–3.12).<sup>17</sup> In the Honolulu aging study, there was no significant relationship between current, former, and never smokers and the development of VaD.<sup>18</sup> Thus, there is still debate on this issue, with our study showing no relationship between tobacco use and VaD.

## Alcohol use

In our study, current alcohol use was a protective factor with an odds ratio of 0.48 (95% CI: 0.31–0.74). Current alcohol use was protective in the overall cohort as well as within the subgroup analysis of females and in those patients <80 years of age. The protective effect seemed strongest in cases younger than 80 years, with an odds ratio of 0.31 (95% CI: 0.15–0.66). Within the overall cohort, there did not appear to be a significant association with either alcohol type or previous alcohol use and VaD. In the subgroups, women seemed to have a protective effect with wine use; however, the remaining subgroups did not have significant values. It appears that current alcohol use, as opposed to previous use, seems to be protective. This could reflect a direct cardiovascular effect of alcohol upon vascular risks. Mild-to-moderate alcohol intake is associated with improved endothelial function.<sup>19</sup> It could also represent better social support in those individuals who drink socially with other individuals.<sup>20</sup> The individuals who drink alcohol also possess a higher functional status than those who do not drink.<sup>21</sup> However, in previous studies, even after adjustment for social economic status and functional

status, those individuals who have a moderate intake of alcohol have increased longevity.<sup>21</sup> In our study, if a patient suffers VaD, it is quite possible that they do not have the means or methods of obtaining alcohol for current use.

Alcohol use has had a mixed picture with vascular disease and with memory problems. Alcohol has a neurotoxic effect upon the central nervous system and in excess, can cause alcohol-related dementia.<sup>22</sup> In a pooled meta-analysis, light-to-moderate alcohol use had a small protective effect for the development of any type of dementia with a relative risk of 0.75 (95% CI: 0.57–0.98). Heavy alcohol use was not protective and was a risk in this meta-analysis.<sup>23</sup> VaD as a specific illness was not evaluated in this meta-analysis. In a large Chinese cohort study, mild-to-moderate alcohol consumption had a larger protective effect for VaD risk with a hazard ratio of 0.31 (95% CI: 0.19–0.51) compared to Alzheimer's disease with a hazard ratio of 0.63 (95% CI: 0.55–0.72). Heavy alcohol use was not protective.<sup>24</sup> In the Canadian Study of Health and Aging, there was no association between weekly alcohol use (beer, wine, or spirits) and the development of VaD. The odds ratios varied between alcohol type; however, the lowest odds ratio was for beer, at 0.61 (95% CI: 0.31–1.26) and was not significant.<sup>25</sup> Thus, the relationship with alcohol use has not shown a consistently protective effect in preventing VaD; however, in aggregate, the studies do trend toward a protective effect.

## Study limitations

There are some limitations with the study. In this matched case-control study, one has the advantages of robust medical records with defined criteria. The agreement between electronic abstraction and nurse abstraction tends to favor nurse abstraction, which was performed in this study.<sup>26</sup> There exists the possibility of missing information which can be an inherent challenge with case-control studies. For the primary outcomes of tobacco or alcohol use, the range of missing information was low at 8–17 (2%–4%) missing records per exposure variable. The type of tobacco or alcohol type had more missing records. However, the records were fairly complete and the subjects filled out questionnaires yearly. The biggest challenge involves the self-report of lifestyle issues such as alcohol use.<sup>27</sup> There may have been a tendency to under-report alcohol or tobacco use to the provider. This could mitigate any real effects or differences between VaD cases and the controls. In case-control studies, the issue of recall bias is also an important one. The lifestyle questionnaires are asked yearly; thus, the risk of recall bias is reduced.

The generalizability of this study to other populations remains an important question. The population of the study was a largely English-speaking white population. The ability to generalize this to other populations and other countries might be problematic. The weight of the evidence that alcohol is protective in vascular disease is growing. However, there are potentially economic, social, and cultural issues that may influence the type and amount of alcohol taken. Thus, the findings of this study are encouraging, but one must be cautious if the local population differs greatly from the one studied.

## Conclusions

Vascular dementia remains a common and daunting problem that affects many adults in developed and developing countries. This matched case-control study found that current alcohol use may actually reflect a potential protective effect of alcohol on the vascular system. Tobacco use (current, previous, ever), along with type of tobacco use, was not associated with VaD status. This lack of association may be related to a survivorship bias. There clearly remains further work to be performed to fully understand all of the risks for vascular dementia in the older population.

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## Disclosure

The authors report no conflicts of interest in this work.

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