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The effects of wine and tobacco consumption on cognitive performance in the elderly: a longitudinal study of relative risk

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Background	Evidence relating to the potentially protective effect of smoking and alcohol consumption in relation to senescent cognitive decline and Alzheimer's disease is inconclusive.
Methods	The relationship between wine and tobacco consumption and cognitive change was assessed within a longitudinal study of normal elderly people showing recent instability in cognitive functioning using an extensive battery of cognitive tests.
Results	While moderate wine consumption was found to be associated with a fourfold diminishing of the risk of Alzheimer's disease (OR = 0.26), as found in other studies, this effect was found to disappear when institutionalization was taken into account. Wine consumption was associated with an increased risk of decline over time in attention and in secondary memory. No protective effect for Alzheimer's disease was found for smoking, although smoking was associated with a decreased risk for decline over time in attentional and visuospatial functioning. No clear combined effect of smoking and drinking was found, even though smoking was found to increase the risk of decline in language performance when adjusted on wine consumption.
Conclusions	There is no evidence to suggest that wine and tobacco consumption may protect against Alzheimer's disease.

Keywords	Alzheimer's disease, smoking, alcohol, cognitive functioning, risk
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Of the many risk factors which have been examined in relation to Alzheimer's disease, the role of smoking and alcohol consumption is amongst the most disputed. A series of studies conducted in the 1980s[1–3] failed to show any significant relationship between smoking or drinking and Alzheimer's disease, although one study[2] was found to show an increased risk of Alzheimer's disease in smokers when education effects were taken into account. It is, however, possible that the exclusion of subjects from these studies with a history of alcoholism or cardiovascular disease may have biased results.

More recent studies which have focused on levels of consumption have demonstrated protective effects for moderate alcohol consumption[4–6] and dose-related protective effects for smoking.[7] These results require further critical examination due to the important public health implications of recommending smoking and drinking for protection against a disease with onset mainly at very high ages, in the face of the very great health hazards that these two behaviours represent throughout the life cycle.

A shortcoming of present studies is that they have not taken into account the interactive effect of smoking plus alcohol consumption, have been unable to establish whether smoking and drinking uniformly affect cognitive change (or whether they may have an impact specifically on cerebral regions affected by Alzheimer's disease), and finally the effect of environment has not been taken into account. This is a potential source of bias as cases of senile dementia may be admitted to institutional care where smoking and drinking is prohibited.

The present study examines wine and smoking-related changes in a wide array of cognitive functions over time in a longitudinal cohort study of the normal elderly with minor cognitive deficits. The 2-year incident rate of senile dementia is high in this population (18%) and it has been possible to not only estimate the relative risk for dementia for wine and tobacco consumers independently and together, but also to examine in greater detail over 3 years the precise areas of cognitive performance which might be affected.

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Subjects

In all, 833 subjects were recruited through a general practitioner research network in the South of France as part of the Eugeria longitudinal study of cognitive ageing.[8] A proxy screening questionnaire on cognitive functioning over the past year was sent to everyone over 60 years in each general practice not meeting DSM III[9] criteria for senile dementia. General practitioners were trained over a 2-day period prior to the study, with remuneration for loss of practice, in the assessment of cognitive decline using a standardized procedure adapted for the general practice setting, and in applying DSM IIIR criteria. The screening instrument, DECO (Détérioration Cognitive Observée), has been shown in previous studies to be highly sensitive to early changes in cognitive functioning due to various causes[10] and is based on degree of change in behaviour over the last year as estimated by a proxy who has had at least monthly contact with the subject over the past 3 years. These subjects constituted at baseline a population of the normal elderly from a representative sample of general practices. All subjects returning questionnaires agreed to participate in the study. However, it is not known whether some subjects did not complete the questionnaire and were lost at this stage.

Of the 833 subjects included in the cross-sectional study, 397 were found to have a score of less than 38 on DECO; 38 being the maximum total score. These subjects were thus considered by an observer to have shown some degree of deterioration in at least one area of cognitive functioning over the past year. These normal 'at risk' subjects were followed over a further 3 years.

Methods

Each subject was visited in their home annually by one of the project interviewers and a computerized neuropsychometric examination was administered. This examination, ECO[8] (Examen Cognitif par Ordinateur) was used to assess working memory, verbal and visuospatial secondary memory, implicit memory, language skills (word and syntax comprehension, naming, verbal fluency, articulation), visuospatial performance (ideational, ideo-motor and constructive apraxia, functional and semantic categorization of visual data, visual reasoning and form perception), and focused and divided attention (visual and auditory modalities). The reliability of ECO sub-tests has been established on a sample of 60 normal and pathological subjects. The theoretical justification for the choice of tests and their development is given in Ritchie *et al.*[8] Overall refusal rates for all subjects through the 3 years of the study was only 5%. This was found to be predominantly due to ill-health or hospitalization, and many subjects continued with the study in the following year.

From the 159 ECO variables, eight summary scores representing six cognitive domains were used in the analysis. The eight summary scores were derived from the mean of the rescaled scores (between 0 and 100):

attention (**att**)—measured by response time on a dual task (simultaneous visual selection and counting of auditory stimuli),

primary memory (**prm**)—(verbal and visual span): assessed by immediate recall of first names which had the highest frequency in the French language 50 years ago, and visual trails of increasing length,

secondary memory (**scm**)—measured by delayed recall of first names and their associated faces, and prose recall,

implicit memory (**imm**)—measured by reference to the number of trials required to recognize previously presented items as compared to novel stimuli reconstructed progressively on the computer screen,

visuospatial ability (**vis)**—measured by reference to two scores; number of correct responses on tasks of shape-matching, semantic and functional categorization and reproduction of three-dimensional figures (**vis2**), and response time on shape, functional and semantic matching tasks (**vis1**),

language (**lan)**—assessed by tests of word and syntax comprehension, naming and verbal fluency. Two scores are derived; total number of correct responses (**lan2**), and word and syntax comprehension response time (**lan1**).

A standardized neurological examination for the diagnosis of psychogeriatric disorder corresponding to both DSM IIIR[11] and International Classification of Diseases—Ninth Revision[12] criteria was carried out in the third year. A semi-structured diagnostic interview was constructed by the study neurologist (JT) based on DSM III criteria and using cognitive assessment methods different from those used within ECO. The diagnosis of dementia was made by applying the diagnostic algorithm of DSM IIIR in conjunction with SPECT (Single Photon Emission Tomography) where available, and the results of biological tests. Information was collected relating to quantity and frequency of tobacco and alcohol consumption using the same short standardized interview as used by Orgogozo *et al.*[6] in the Bordeaux study with additional questions differentiating past and present consumption. The study interviewers did not have information relating to alcohol and tobacco use. Interviewers were trained over a 2-week period at the beginning of the study and at approximately 6-month intervals were observed and asked to perform double examinations in order to assure adequate inter-interviewer reliability. Reliability is further enhanced in this study through the automatic registration of most of the results of cognitive testing via a tactile screen.

Results

Age and education were recoded as dichotomous variables for the present analysis (<75 years and 75+; primary or secondary education and baccalaureate +). Complete data sets were available for 225 subjects among the 259 subjects who completed the three waves of the study and were still alive at the time of collection of data on alcohol and tobacco consumption in the final year. Alcohol consumption was almost exclusively of wine so that adjustment for higher alcohol content was not considered necessary. Wine use was predominantly moderate (3–4 wine glasses per day), with only six subjects exceeding this amount. Subjects are thus coded as either non-drinkers or drinkers (⩾1/4 litre). Smokers are classified as non-smokers and smokers, with the latter category including former smokers (within the past

10 years). Dichotomous variables for wine and tobacco consumption were used to enable comparisons with other studies. Given the small variance in the range of responses this did not lead to significant information loss.

Decline in cognitive functioning was defined as a drop of >10% (approximately one standard deviation) in a given cognitive function. Observed declines over any one-year interval in the study or over all three waves of the study were categorized for the whole study in two ways : (i) at least one of any decline observed (Dec-event), (ii) at least any one-year interval decline plus decline over all three waves (Dec-continuous). This latter classification has been used to differentiate people showing either an improvement in any one year or an overall slow decline from subjects showing significant progressive deterioration. Subjects with significant on-going decline are thus clearly differentiated from those manifesting temporary drops in performance. Due to the non-normality of the cognitive scores, Mann-Whitney U statistics have been used both on total scores and on the residuals derived from the analysis of variance model (least squares residuals estimations) in order to take into account age, sex, and education effects. Odds ratios (OR) have been calculated through logistic regression both with and without sex, age, institutionalization and education adjustments. Given the relatively small sample size and large variance in the cognitive scores, results have been reported up to a *P*-value of 0.1.

Demographic features and tobacco and wine consumption for the subjects in the study are presented in Table 1.

Wine consumption and smoking as risk factors for Alzheimer's disease

Subjects below 75 were more likely to smoke (47%), than those over 75 (31%, $P < 0.01$), but no significant age effect was found for wine consumption. Men were found to be more likely to smoke (77%) than women (25%, $P < 0.001$) and also to be more frequently moderate consumers of wine (71%) than women (40%, $P < 0.0001$). Education effects were also noted with regard to smoking; highly educated subjects being more likely to smoke (48%) than people with low education (25%, $P < 0.01$), but no education effects were observed with regard to wine consumption. Smokers were found to drink slightly more (57%) than subjects who do not smoke (45%, $P = 0.06$).

The OR for developing Alzheimer's disease related to wine consumption is 0.26 (95% confidence interval [CI] : 0.05–1.3, $P = 0.09$), 0.25 (95% CI : 0.05–1.3, $P = 0.10$) adjusted by smoking, and 0.13 (95% CI : 0.04–1.2, $P = 0.08$) adjusted by age and education. The protective effect is somewhat improved when adjusted for age and education. On the other hand adjustment by place of residence (community versus institutionalization) has a significant effect, yielding an adjusted OR of 10.7 (95% CI : 2–56, $P = 0.005$), such that the observed protective effect of wine consumption becomes non-significant. Calculation of the OR for Alzheimer's disease for smoking adjusting by the same variables gave no significant results.

The effect of wine and smoking on cognitive functioning over time

While drinkers had higher performance on attention tasks in the second year of the study ($P = 0.05$, U-Mann-Whitney tested on least squares residuals according to age, sex and education adjustement), they also showed a significantly higher drop during the following year ($P = 0.03$). Most of the differences between smokers and non-smokers on each of the eight cognitive scores disappeared after adjustment, however smokers were seen to have a lower overall decline in performance on response time on visuospatial tasks ($P = 0.04$). They were observed to have, however, a lower performance at baseline for this latter score ($P = 0.01$).

The percentage of subjects showing decline at any year interval or overall (Dec-event) is given in Table 2 according to consumption. Drinkers who do not smoke were seen to have a higher rate of decline in attention (50.9%) than other categories (28.1–37%, $P = 0.07$).

No significant overall effect for wine or smoking was found on this contingency table of 432 potential decline events, however, the first dimension of a Correspondence Analysis, accounting for 65.6% of the χ^2, was found to be significant ($P = 0.005$). This dimension opposed on the one hand 'smoking' and 'smoking plus wine' associated with a decline in language and primary memory, and on the other hand, wine associated with a decline in attention, and reaction time in visuospatial analysis (Figure 1).

Odds ratios were calculated for smokers and drinkers for decline over a year or on the overall study (Dec-event) and for continued decline (Dec-continuous). Moderate drinkers were found to have a significantly higher risk of progressive decline (Dec-continuous) on tasks of attention (adjusted OR = 2.2, 95% CI : 1–5, $P = 0.06$) and secondary memory (adjusted OR = 3.3, 95% CI : 0.8–13, $P = 0.09$). Smokers, on the other hand, were seen to have a diminished risk of decline (Dec-event) on attention tasks (OR = 0.54, 95% CI : 0.3–0.97, $P = 0.04$) and visuospatial task response time but not on number of responses correct on visuospatial tasks (adjusted OR = 0.51, 95% CI : 0.2–1.2, $P = 0.1$). Smokers also had a diminished risk of continued decline (Dec-continuous) on visuospatial tasks reaction time (adjusted OR = 0.28, 95% CI : 0.07–1.2, $P = 0.08$). Risk of decline for combined wine and tobacco consumption was estimated using a logistic regression model. This generally gave similar results to those cited above except that it can be seen that adjusting by wine consumption gave rise to a fourfold risk

Table 1 Sociodemographic characteristics of subjects by wine and tobacco consumption

Age		None	Tobacco only	Wine only	Both	Total N = 225	Column %
Below 75	Low education	19 (38%)	10 (20%)	13 (26%)	8 (16%)	50	22%
	High education	21 (29%)	15 (21%)	12 (17%)	24 (33%)	72	32%
75+	Low Education	15 (44%)	0 (0%)	16 (47%)	3 (9%)	34	15%
	High Education	21 (31%)	13 (19%)	19 (27%)	16 (23%)	69	31%

Frequency (rounded row per cent).

Table 2 Description of the declines (Dec-event) according to tobacco and wine consumption

Cognitive function		None	Tobacco only	Wine only	Both	Total
	N=	73	32	55	48	208
att *	N	27	9	28	14	78
	%	37.0	28.1	50.9	29.2	37.5
lan1	N	17	9	15	14	55
	%	23.3	28.1	27.3	29.2	26.4
lan2	N	21	8	11	15	55
	%	28.8	25.0	20.0	31.3	26.4
prm	N	26	16	24	23	89
	%	35.6	50.0	43.6	47.9	42.8
scm	N	12	3	11	7	33
	%	16.4	9.4	20.0	14.6	15.9
imm	N	15	6	10	8	39
	%	20.5	18.8	18.2	16.7	18.8
vis1	N	20	6	17	9	52
	%	29.4	18.8	31.5	19.1	25.9
vis2	N	12	3	7	9	31
	%	16.9	9.7	12.7	18.8	15.1
Average		150/73 = 2.05	60/32 = 1.87	123/55 = 2.23	99/48 = 2.06	432/208 = 2.07

* χ^2 test $P = 0.07$, the others are not significant $P > 0.10$.

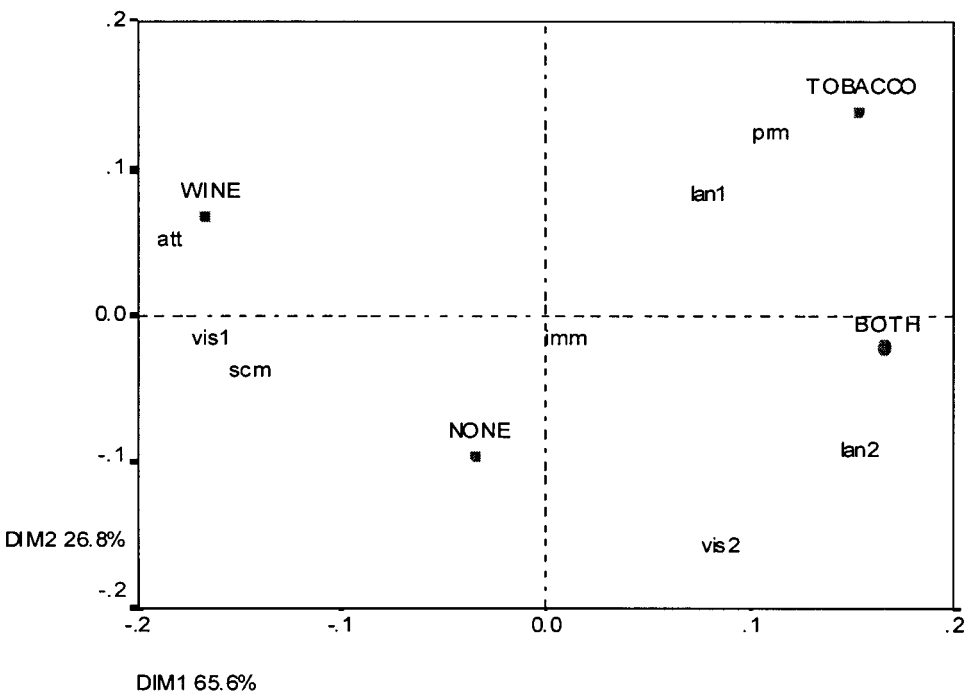

Figure 1 Correspondence analysis of decline by wine and tobacco consumption (Table 2)

of language impairment for smokers (Dec-continuous, adjusted OR = 3.8, 95% CI : 0.8–18, $P = 0.1$).

Too few subjects had both apolipoprotein-E phenotype data and complete information on alcohol and tobacco consumption available to be able to adequately take this factor into account in the analysis. Apo-e4 subjects were observed however, to have fourfold risk of decline in secondary memory (Dec-event, OR = 4.3, 95% CI : 1.1–16, $P = 0.04$).

Discussion

Examination of the risk of smoking and wine consumption for Alzheimer's disease shows a protective effect for wine only which is of the same order (fourfold) as that found by Orgogozo *et al.*[6] in the Bordeaux study. When institutionalization is taken into account, however, this 'protective' effect is seen to disappear suggesting that it may have been, at least in part, due to the fact

that people with Alzheimer's disease may often find themselves in living conditions where they are prevented from drinking.

Examination of the effect of smoking and alcohol consumption on cognitive decline over time in a vulnerable group of normal elderly demonstrates that wine increases the risk of decline in attention and secondary memory. The data available did not allow us a combined analysis of wine factor and apolipoprotein-e4, but an increased risk of secondary memory decline for the latter suggests a possible association. Taking into account apo-e4 in risk calculation for Alzheimer's disease due to wine or tobacco consumption may modify the results. On the other hand smoking was found to decrease the risk for decline on tasks of attention and visuospatial analysis in keeping with well-documented findings of the stimulant effect of nicotine, which has also been associated with reduction of amyloid toxicity.[13] Smoking may thus play a part in reducing the attentional deficits and apraxias associated with early stage Alzheimer's disease, and perhaps thus increases time to onset, without preventing the disease itself. Tobacco and wine consumption may have an antagonistic effect (Figure 1) on the risk of decline in language functioning, as the single variable association (smoking and decline in language) reached significance only when adjusted on wine consumption.

Unfortunately although vascular risk factors have been examined in the Eugéria study, numbers would be too small to assess the mediating effect they might have through for example, decreasing the risk of senile dementia only in those with a high vascular risk. Due to the relatively small sample size in this study and difficulty in assessing dose effects, the results of the study certainly need to be confirmed. The results are also limited in that only 3-year risk of Alzheimer's disease is assessed. The risk related to wine and smoking for people developing a much slower form of the disease is unknown and requires investigation by longer-term epidemiological studies of dementia.

Conclusion

A longitudinal study of the normal elderly with sub-clinical levels of cognitive change demonstrates a reduced risk of Alzheimer's disease related to moderate intake of wine. This effect disappears when institutionalization is taken into account. Wine is seen to increase the risk of decline in memory and attentional abilities while smoking has a mildly protective effect against decline in attentional and visuospatial functioning. Studies with larger number of subjects are needed to confirm combined effects of smoking and drinking, and their possible interaction with genetic factors on cognitive decline of the elderly and the development of dementia.

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