Dementia associated with alcohol and other drug use

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ABSTRACT

The acute use of alcohol and several other licit and illicit drugs can affect mental state and cognitive function. The chronic use of certain drugs may also increase the risk of cognitive impairment and perhaps dementia in later life. This paper focuses on the long-term cognitive consequences of using alcohol, benzodiazepines, tobacco and cannabis. Currently available evidence indicates that mild to moderate alcohol consumption is not associated with increased risk of cognitive decline and may in fact have a protective effect against dementia, although heavy, long-term consumption is likely to have a negative impact on cognitive function. The degree that alcohol-related cognitive impairment must reach to be classified as dementia is currently obscure. Longer-term smoking is associated with increased risk of cognitive impairment and possibly dementia. The chronic use of benzodiazepines has been associated with increased risk of cognitive impairment but information relating to dementia remains inconclusive. The chronic use of cannabis may impair intellectual abilities but data on this topic remain sparse and difficult to interpret. In conclusion, there is evidence that some drugs contribute to the causal pathway that leads to the development of cognitive impairment but currently available data do not support the introduction of a separate diagnostic category of drug-induced dementia (such as alcohol-related dementia). Health promotion programs designed to decrease tobacco smoking and “harmful” alcohol use (and possibly other drug use) may decrease the burden of cognitive impairment and perhaps dementia in later life.

Key words: alcohol, tobacco, benzodiazepine, cannabis, cognitive impairment, dementia

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Introduction

Although dementia is considered to be a health issue of later life, drug and alcohol use is often seen as a problem of adolescents and younger adults. This may partly explain the relative dearth of information on the cognitive consequences of drug use, particularly in relation to its potential contribution towards the development of cognitive impairment and dementia. This paper reviews the association between the use of alcohol, tobacco, benzodiazepines and cannabis, and cognitive performance and risk of dementia. A brief section on the cognitive consequences of using other drugs is also presented.

Alcohol, cognitive impairment and dementia

Alcohol use is associated with acute and non-acute effects on cognitive function. The acute consumption of alcohol leads to slowness of mentation, increased reaction time and, with increasing severity of intoxication, impaired memory, attentional deficits, delirium and coma (Grant, 1987). The long-term cognitive consequences of regular alcohol use are less clear.

Alcohol and cognitive function

Four prospective studies have explored the effects of exposure to alcohol on cognitive attainment over time. Two reported no consistent association between alcohol consumption and cognitive decline (Edelstein et al., 1998; Herbert et al., 1993) and two found that alcohol use may reduce the risk of cognitive impairment (Launer et al., 1996; Leroi et al., 2002). The longest of these follow-up studies was based on a sub-analysis of the Baltimore arm of the Epidemiologic Catchment Area study. Leroi et al. (2002) examined 1488 subjects from the original inception cohort of 3481 people who had completed their baseline evaluation in 1982. Subjects who consumed alcohol at baseline did not experience a greater decline in Mini-mental State Examination (MMSE) scores than non-drinkers after 11.5 years, regardless of the amount of alcohol consumed (from occasional drinking to regular consumption of more than four drinks per day for more than 20 days of the month). This study highlights some of the problems associated with many observational studies: (1) there was a significant loss of participants to follow-up, which might have introduced survivorship bias (e.g. alcohol consumers who were cognitively impaired might have been preferentially lost to follow-up); (2) more than half of the cohort was younger than 40 years of age and therefore would have been less likely to experience cognitive decline than older adults; (3) there was a ceiling effect associated with the use of the MMSE; and (4) subjects who consume large amounts of alcohol are probably less likely to volunteer/agree to be part of these studies (selection bias).
Cross-sectional studies investigating the association between alcohol and cognitive function have been particularly prone to selection bias (Zinn et al., 2003; Zuccala et al., 2001), but some have produced evidence in support of the idea that the period of alcohol abstinence may be relevant to cognitive performance. Munro et al. (2000) reported that 18 older adults who had been abstinent for less than 6 months had consistently lower scores on a comprehensive neuropsychological battery than 17 controls, whereas subjects who had been abstinent for more than 6 months were only worse than controls on measures of verbal and visual memory, and verbal fluency.

**Alcohol and dementia**

The results of observational studies suggest that light to moderate alcohol use is not associated with an increased risk of Alzheimer’s disease (AD) (Huang et al., 2002; Lindsay et al., 2002; Mukamal et al., 2003; Orgogozo et al., 1997) or vascular dementia (VaD) (Ruitenberg et al., 2002). In fact, preliminary evidence indicates that low-level alcohol use, when compared to either no alcohol or moderate/high levels of alcohol consumption, might be associated with decreased risk of dementia (Table 1).

The first study to prospectively investigate the association between alcohol consumption and dementia (Orgogozo et al., 1997) reported that older adults who drank three or four glasses of wine per day were less likely to develop dementia after 3 years of follow-up than nondrinkers \( \text{OR} = 0.19 \). Those who drank one or two \( \text{OR} = 0.55 \) or three or four glasses of wine per day \( \text{OR} = 0.28 \) were also less likely to develop AD. The consumption of more than four glasses of wine per day had no obvious effect on the risk of dementia in this cohort (see Table 1). Subsequent studies have produced similar results (Ruitenberg et al., 2002).

Mukamal et al. (2003) reported that the risk of dementia for older adults consuming 1–6 standard drinks weekly \( \text{OR} = 0.46 \) was less than for those consuming higher levels \( \text{OR} = 0.64 \) and \( 1.22 \) for 7–13 and \( > 13 \) standard drinks weekly, respectively). This risk was also less than that for those consuming less than one standard drink weekly \( \text{OR} = 0.65 \), suggesting that moderate alcohol consumption was associated with a lower risk of incident dementia among older adults. The protective action of moderate alcohol use may be more pronounced among persons without an apolipoprotein E (APOE) \( \varepsilon4 \) allele, as subjects with an APOE \( \varepsilon4 \) allele were found to be prone to the deleterious effects of high alcohol intake (Mukamal et al., 2003).

**Alcohol and decreased risk of dementia: potential mechanisms**

Several factors might affect the association between alcohol consumption and risk of dementia. First, moderate alcohol use, compared to alcohol abstinence,
Table 1. Summary of prospective studies investigating the association between alcohol consumption and risk of dementia

<table>
<thead>
<tr>
<th>STUDY</th>
<th>SAMPLE SIZE</th>
<th>DURATION OF FOLLOW-UP (YEARS)</th>
<th>LIGHT ALCOHOL USE</th>
<th>MODERATE ALCOHOL USE</th>
<th>HEAVY ALCOHOL USE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orgogozo et al. (1997)</td>
<td>2273</td>
<td>3</td>
<td>0.81 (0.50–1.30)</td>
<td>0.19 (0.05–0.66)</td>
<td>0.31 (0.04–2.42)</td>
</tr>
<tr>
<td>(odds ratio, 95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lindsay et al. (2002)</td>
<td>4088</td>
<td>5</td>
<td>0.49* (0.28–0.88)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(odds ratio, 95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ruitenberg et al. (2002)</td>
<td>5395</td>
<td>6</td>
<td>0.58† (0.38–0.90)</td>
<td>1.00 (0.39–2.59)</td>
<td></td>
</tr>
<tr>
<td>(hazard ratio, 95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Truelsen et al. (2002)</td>
<td>1709</td>
<td>15</td>
<td>0.81 (0.39–1.72)</td>
<td>1.74 (0.74–4.07)</td>
<td>1.29 (0.53–3.15)</td>
</tr>
<tr>
<td>(odds ratio, 95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Huang et al. (2002)</td>
<td>402</td>
<td>6</td>
<td>0.6† (0.4–1.0)</td>
<td></td>
<td>–</td>
</tr>
<tr>
<td>(relative risk, 95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mukamal et al. (2003)</td>
<td>746</td>
<td>5</td>
<td>0.46‡ (0.27–0.77)</td>
<td>0.64 (0.36–1.13)</td>
<td>1.22 (0.60–2.49)</td>
</tr>
<tr>
<td>(odds ratio, 95% CI)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Luchsinger et al. (2004)</td>
<td>981</td>
<td>4</td>
<td>0.52*† (0.34–0.80)</td>
<td></td>
<td>–</td>
</tr>
<tr>
<td>(hazard ratio, 95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CI = confidence interval.
* Significant for wine but not for beer or liquor.
† Light to moderate alcohol use.
‡ Consumption of less than one standard drink; OR = 0.65, 95% CI 0.41–1.02.
is associated with a lower prevalence of silent infarcts and white matter disease on magnetic resonance imaging (MRI) studies (Mukamal et al., 2001). Second, alcohol might act by reducing cardiovascular risk factors through an inhibitory effect of ethanol on platelet aggregation (Fenn and Littleton, 1982) or through alteration of the serum lipid profile (Miller et al., 1988). Third, alcohol may act directly on cognition by increasing release of acetylcholine in the hippocampus, which is known to facilitate learning and memory (Perry et al., 1999). Fourth, alcohol may suppress APOE binding to beta-amyloid, or improve the lipid profile of APOE ε4 carriers who have low concentrations of high-density lipoprotein (HDL) and high concentrations of low-density lipoprotein (LDL) cholesterol (Strittmatter et al., 1993).

Alcohol abuse and increased risk of dementia

Cross-sectional studies assessing the effect of heavy, frequent alcohol consumption on the risk of dementia have consistently shown increased risk of dementia, but these studies may be subject to bias. Thomas and Rockwood (2001), for example, reported the results of a cross-sectional analysis of the Canadian Study of Health and Aging that included 2764/10 268 older adults. Subjects with questionable or definite alcohol abuse were more likely to have cognitive impairment or dementia than older adults with no such a history [OR = 1.5, 95% confidence interval (CI) = 1.2–2.0]. However, subjects with a history of alcohol abuse (questionable or definite) were more likely to have died during the subsequent 18 months (OR = 1.6, 95% CI = 1.1–2.2), introducing survivorship bias into these results and raising questions about their validity.

Alcohol and cognitive impairment: potential pathogenetic mechanisms

Results of neuroimaging studies indicate that people with alcohol-related disorders have thinner gyri and wider sulci, as well as loss of gray and white matter (Ding et al., 2004), with neuropathological findings confirming that the brains of alcoholic patients are smaller, lighter and show substantial white matter loss (Harper et al., 2003). Crews et al. (2004) showed that alcohol-induced oxidative stress and inflammatory response lead to neuronal loss (particularly in the limbic system), while alcohol withdrawal induces hippocampal neurodegeneration as a result of enhanced glutamate activity.

Reduction in brain volume is unlikely to be the result of simple dehydration, but rather due to alcohol-induced reduction of the dendritic arbor, a precursor of cellular death, which is possibly reversible in the early stages of alcohol neurotoxicity (Harper and Corbett, 1990). From a treatment perspective, abstainers may show some reversal of this neuropathology, while those who continue to use alcohol do not (Shear et al., 1994).
Some authors have suggested that a large proportion of “alcohol dementia” cases are probably unrecognized cases of Wernicke–Korsakoff syndrome, with the remainder possibly attributed to other conditions, including chronic hepatocerebral degeneration, communicating hydrocephalus, AD, ischemic infarction (Torvick et al., 1982; Victor and Adams, 1985) and VaD (Lishman, 1990). This line of argument is that alcohol per se is unlikely to be the causal agent of dementia, but is instead a probable contributing factor that can only cause or result in dementia when acting with other agents (i.e. thiamine insufficiency, chronic hepatocerebral degeneration, communicating hydrocephalus, AD, ischemic infarction). For example, people who drink excessively may develop nutritional deficiencies such as folate and vitamin B12 deficiency (Laufer et al., 2004), which in turn may increase the risk of cognitive impairment and dementia. The consumption of spirits reduces plasma levels of folate but does not significantly change the concentration of B12 (Van der Gaag et al., 2000). However, both red wine and spirits (but not beer) were associated with a significant increase in total plasma homocysteine (8–9%).

High plasma homocysteine is an accepted risk factor for strokes, dementia and AD (Eikelboom et al., 2000; Seshadri et al., 2002). High plasma homocysteine is also associated with increased brain atrophy (Sachdev et al., 2002) and, in the case of patients with alcohol dependence, with hippocampal atrophy as well (Bleich et al., 2003).

Excessive alcohol consumption has been shown to double the risk of strokes [relative risk (RR) = 2.1, 95% CI = 1.2–3.8], which, in turn, substantially increases the risk of cognitive impairment and dementia (Ivan et al., 2004; Starkstein and Almeida, 2003). Other common factors associated with alcoholism, such as smoking, sedentary lifestyle, diabetes and hypertension, increase the risk of cerebrovascular disease, cognitive impairment and dementia (Almeida et al., 2002; Lautenschlager et al., 2003; Ruidavets et al., 2004).

As noted above, the APOE genotype is yet another factor that may modulate the cognitive outcomes associated with alcohol use. Dufoil et al. (2000) reported APOE ε4 carriers who consumed five or more glasses of alcohol per day were at increased risk of cognitive deterioration over a follow-up period of 4 years compared to nondrinkers who were noncarriers (RR = 8.3, 95% CI = 1.0–66.0).

The association between alcohol consumption and traumatic brain injury (TBI) should also be recognized. Approximately 50% of people hospitalized for TBI are intoxicated with alcohol at the time of admission (and the accident), with 60% of cases having a history of alcohol or other drug abuse (Bombardier et al., 2002; Corrigan, 1995).

Finally, the relationship between Wernicke–Korsakoff syndrome and cognitive decline is well established. Wernicke’s encephalopathy (WE) represents the abrupt clinical manifestation of severe thiamine deficiency and is characterized
by nystagmus, ophthalmoplegia (conjugated gaze palsies), gait ataxia and confusion. Although WE is most prevalent among persons with alcoholism, it is not caused by alcohol per se but by a thiamine diphosphate deficiency. This biologically active form of thiamine (vitamin B1) is a cofactor in several enzyme reactions involved in the biosynthesis of cell constituents, neurotransmitters, production of antioxidants, catabolism of carbohydrates and synthesis of nucleic acid precursors (Singleton and Martin, 2001). A large percentage of WE cases (84%) develop Korsakoff syndrome (KS), which is characterized by marked memory impairment with relative preservation of other cognitive functions. Typically, patients are unable to learn new information, but may also have some difficulty remembering past events. Severe thiamine deficiency, and the consequent Wernicke–Korsakoff syndrome, is associated with lesions to the mamillary bodies, thalamus, hypothalamus, brainstem and cerebellum (particularly the vermis) (Harper, 1998). MRI studies suggest that thiamine insufficiency causes neurological lesions in both diencephalic and cortical regions by targeting areas such as mamillary bodies, whereas longer-term alcoholism produces additional damage to the brain (Butters, 1985; Charness and DeLaPaz, 1987; Lishman, 1990).

Alcohol per se may not cause dementia

It has been suggested that subcortical lesions caused by alcohol may be sufficient to explain cognitive impairment but not the dementia observed in “alcoholic-related dementia” (ARD). Thus, it is likely that alcohol only “causes” dementia as a contributing factor when associated with other disease entities. However, it also has been argued that the role of alcohol in cognitive dysfunction may be significantly underestimated because its contribution and associated cognitive impairment may be labeled under another more obvious coexisting diagnosis. Accordingly, some investigators have suggested that the contribution of ARD is much more frequent than previously suspected and might account for 20–25% of all cases with dementia (Carlen et al., 1994; Lishman, 1998).

Such observations served as the basis for the introduction of diagnostic criteria for ARD by Oslin et al. (1998) (Table 2). However, these criteria are based on an arbitrary level and period of alcohol consumption without a well-established neuropathological basis. The clinical validation study reported by Oslin and Cary (2003) was based on the premise that people with ARD do not show the same rate of cognitive and functional decline experienced by patients with AD. In a 2-year follow-up study of 16 people with ARD and 26 with AD, cognitive status was monitored with the MMSE and functional capacity with the Physical Self-Maintenance Scale (PSMS). Subjects with ARD did not show any obvious deterioration in MMSE or PSMS scores but, as predicted, patients with AD did. Unfortunately, patients with AD had significantly worse cognitive and functional
Table 2. Diagnostic criteria for alcohol-related dementia (modified from Oslin et al., 1998)

<table>
<thead>
<tr>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dementia</strong></td>
</tr>
<tr>
<td>Decline of cognitive abilities that interfere with social and occupational functioning. DSM-IV requires deterioration of memory and at least one other higher cortical function, and such cognitive changes cannot be explained by delirium or substance intoxication or withdrawal.</td>
</tr>
</tbody>
</table>

| **Definite alcohol-related dementia**         |
| No acceptable criteria currently available.   |

| **Probable alcohol-related dementia**         |
| A. Criteria should include both:              |
| 1. Clinical diagnosis of dementia at least 60 days after exposure to alcohol |
| 2. Significant alcohol use – 35 or more standard drinks per week for men and 28 or more for women for 5 years or more. The onset of dementia must take place within a 3-year period of significant alcohol use |
| B. The diagnosis is supported by:            |
| 1. Alcohol-related hepatic, pancreatic, gastrointestinal, cardiovascular, renal disease or other end-organ damage |
| 2. Ataxia or peripheral sensory polyneuropathy not attributed to other causes |
| 3. Stable or improved cognitive function after 60 days of alcohol abstinence |
| 4. Neuroimaging evidence of decreased sulcal or ventricular dilation after 60 days of alcohol abstinence |
| 5. Neuroimaging evidence of cerebellar atrophy, especially the vermis |
| C. Diagnosis is less likely if there is:      |
| 1. Impairment of language                    |
| 2. Focal neurological signs or symptoms (except ataxia or peripheral sensory polyneuropathy) |
| 3. Neuroimaging evidence of cortical or subcortical infarction, subdural hematoma or other focal neuropathology |
| 4. High Hachinski Ischemic Score             |
| D. The following are neither supportive nor unlikely associations of alcohol-related dementia: |
| 1. Neuroimaging evidence of cerebral cortical atrophy |
| 2. Neuroimaging evidence of periventricular or deep white matter lesions |
| 3. Apolipoprotein E ε4 genotype              |

| **Possible alcohol-related dementia**         |
| 1. The period of significant alcohol use occurred more than 3 years but less than 10 years prior to the onset of dementia, or |
| 2. The average significant consumption of alcohol of 21 standard drinks per week for men and 14 for women for 5 years. The onset of dementia must take place within a 3-year period of significant alcohol use |

| **Mixed dementia**                           |
| This diagnosis is to be used when more than one cause of dementia is apparent. |

| **Alcohol as a contributing factor for dementia** |
| To be used whenever alcohol is used, but not to the degree required or within the timeframe that is necessary to establish the diagnosis of possible or probable alcohol-related dementia. This “qualifier” does not exclude the diagnosis of probable Alzheimer’s disease or vascular dementia. |
scores than subjects with ARD at the time of study entry, so that the direct comparison of these two groups of patients during follow-up was likely to be flawed. Thus the question of existence of a “true alcoholic dementia” continues to be debated and requires further investigation.

**Tobacco, cognitive impairment and dementia**

The cholinergic system is thought to play a significant role in the modulation of memory (Perry et al., 1982) and has therefore been a major target of therapeutic interventions for dementia and AD. Smoking boosts cholinergic activity through the delivery of nicotine, which in turn improves certain aspects of cognitive function in older adults, both with and without AD (Rezvani and Levin, 2001). However, evidence is emerging that chronic tobacco smoking may not be associated with improved cognitive abilities. For example, Ernst et al. (2001) showed that the cognitive performance, particularly working memory, of smokers did not benefit from the administration of oral nicotine, whereas that of nonsmokers did.

**Case–control studies**

A significant number of case–control studies have consistently reported that smoking decreases the risk of dementia (Lee, 1994) and AD (van Duijn et al., 1994). Three reviews (Lee, 1994; Graves et al., 1991; van Duijn et al., 1994) indicate that ever smoking is associated with decreased risk of AD. For example, Lee (1994), in a review of 19 case–control studies, found that ever smoking is associated with decreased risk of AD (OR = 0.64, 95% CI = 0.54 to 0.76) compared with an OR of 0.8 (95% CI = 0.6 to 1.0) reported by van Duijn et al. (1994).

However, it is becoming increasingly clear that the results reported by case–control studies are an artefact of survival bias rather than a true protective effect of smoking (Riggs, 1993). Wang et al., (1999), for example, found that history of smoking was associated with increased mortality among patients with dementia [hazard ratio (HR) = 3.5, CI = 1.4 to 8.8], but not controls (HR = 0.8, CI = 0.5 to 1.2). Hence, smokers who develop dementia were eliminated earlier from the population and underrepresented in cross-sectional samples.

**Cohort studies**

Cohort studies consistently suggest an association in the opposite direction of that reported by case–control studies; that is, smoking increases the risk of AD (Doll et al., 2000; Herbert et al., 1992; Hirayama, 1992; Katzman et al., 1989; Launer et al., 1999; Lindsay et al., 2002; Merchant et al., 1999; Ott et al., 1998;
Table 3. Summary of cohort studies investigating the association between smoking and Alzheimer’s disease (AD)

<table>
<thead>
<tr>
<th>STUDY</th>
<th>COHORT, N</th>
<th>NUMBER OF INCIDENT CASES OF AD WITH INFORMATION ABOUT SMOKING HABITS</th>
<th>RR</th>
<th>CI</th>
<th>SOURCE OF COHORT</th>
<th>DURATION OF FOLLOW-UP</th>
<th>EXPOSURE</th>
<th>DIAGNOSIS OF AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Katzman et al. 1989</td>
<td>434</td>
<td>32</td>
<td>0.27</td>
<td>0.11 to 0.61</td>
<td>Volunteers</td>
<td>Unclear, possibly 3 to 5 years</td>
<td>Current or past smoking</td>
<td>NINCDS-ADRDA criteria for probable AD</td>
</tr>
<tr>
<td>Hebert et al. (1992)</td>
<td>513</td>
<td>76</td>
<td>0.7*</td>
<td>0.3 to 1.4*</td>
<td>Community</td>
<td>4.7 years</td>
<td>Ever smoked</td>
<td>NINCDS-ADRDA criteria for probable AD</td>
</tr>
<tr>
<td>Hirayama (1992)</td>
<td>265118</td>
<td>120 (death certificates)</td>
<td>1.61</td>
<td>1.10 to 2.38</td>
<td>Community</td>
<td>Up to 27 years (until death)</td>
<td>Daily, occasionally, ex-smoker, never smoker</td>
<td>Senile dementia (criteria used for diagnosis was unclear)</td>
</tr>
<tr>
<td>Ott et al. (1998)</td>
<td>6870</td>
<td>105</td>
<td>1.70</td>
<td>1.00 to 2.40</td>
<td>Community</td>
<td>2 years</td>
<td>Never, ever, current</td>
<td>DSM-III-R</td>
</tr>
<tr>
<td>Launer et al. (1999)</td>
<td>16334</td>
<td>277</td>
<td>1.61</td>
<td>1.10 to 2.38</td>
<td>Four different European community cohorts</td>
<td>Rates estimated per 5-year band</td>
<td>Ever smoked</td>
<td>NINCDS-ADRDA criteria for possible or probable AD</td>
</tr>
<tr>
<td>Merchant et al. (1999)</td>
<td>2128 (920 at risk)</td>
<td>142</td>
<td>1.02</td>
<td>0.60 to 1.50</td>
<td>Medicare recipients of a defined area</td>
<td>2 years on average</td>
<td>Ever smoking cigarettes, pipes or cigars</td>
<td>NINCDS-ADRDA criteria for possible or probable AD</td>
</tr>
<tr>
<td>Wang et al. (1999)</td>
<td>343</td>
<td>34</td>
<td>1.1*</td>
<td>0.5 to 2.4*</td>
<td>Community</td>
<td>3 years</td>
<td>Never, ever, current</td>
<td>DSM-III-R</td>
</tr>
<tr>
<td>Dolli et al. (2000)</td>
<td>24133 (death certificates)</td>
<td>370</td>
<td>0.99</td>
<td>0.78 to 1.25</td>
<td>Male British doctors</td>
<td>From 1950s until death</td>
<td>Never, ever, continuing smokers</td>
<td>Based on death certificates</td>
</tr>
<tr>
<td>Lindsay et al. (2002)</td>
<td>4088</td>
<td>194</td>
<td>0.82*†</td>
<td>0.57–1.17†</td>
<td>Canada community</td>
<td>5 years</td>
<td>Never, ever</td>
<td>Dementia DSM-IV AD</td>
</tr>
<tr>
<td>Tyas et al. (2003)</td>
<td>3232</td>
<td>79</td>
<td>1.27†</td>
<td>0.94–1.73†</td>
<td>Hawaii community (males)</td>
<td>29 years</td>
<td>Ever, former, current</td>
<td>Dementia DSM-III-AD</td>
</tr>
</tbody>
</table>

RR = relative risk; CI = confidence interval; NINCDS-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke – the Alzheimer’s Disease and Related Disorders Association.

*Ratio adjusted for age, gender and education. †Ratio adjusted for age, education and apolipoprotein ε4 allele. ‡Risk ratio from odds ratio under rare disease assumption.
Tyas \textit{et al}., 2003; Wang \textit{et al}., 1999) (Table 3). This association is particularly strong when exposure to tobacco is recorded in the most reliable way possible, namely current smoking at the beginning of follow-up.

We found support for this negative relationship between smoking and AD in a meta-analysis of published cohort studies (Almeida \textit{et al}., 2002). The overall RR of AD among ever smokers was 1.10 (CI = 0.94 to 1.29) in a total number of 43,885 subjects. Further analysis was performed, excluding studies with fewer than 10 patients with AD who were smokers (Katzman \textit{et al}., 1989), or whose description of the diagnosis of AD was unclear (Hirayama, 1992). The overall RR (Doll \textit{et al}., 2000; Launer \textit{et al}., 1999; Merchant \textit{et al}., 1999; Wang \textit{et al}., 1999) was 1.12 (CI = 0.93 to 1.34). Finally, data were pooled from cohort studies that described the number of subjects who were smokers at baseline and later developed AD (Launer \textit{et al}., 1999; Merchant \textit{et al}., 1999): the RR was 1.99 (CI = 1.33 to 2.98).

Increased risk of smoking-associated cognitive impairment has recently been supported by one of the largest cohort studies to date, the European Community Concerted Action Epidemiology of Dementia (EURODEM) study. This initiative, comprising four smaller studies from Denmark, France, the Netherlands and the U.K., each with substantial cohorts, confirmed that smoking accelerates cognitive decline in older adults without dementia (Ott \textit{et al}., 2004). Cognitive decline among former smokers was less pronounced than for current smokers, suggesting that some of the cognitive impairment associated with smoking may be reversible.

The increased risk of cognitive impairment and dementia associated with smoking is not unexpected. Smoking is a well-established risk factor for strokes (Jamrozik \textit{et al}., 1994) and, consequently, VaD. In addition, there is now evidence that smoking increases total plasma homocysteine (Bazzano \textit{et al}., 2003), and increased total plasma homocysteine may be associated with an increased risk of strokes, dementia and AD (Eikelboom \textit{et al}., 2000; Seshadri \textit{et al}., 2002).

**Benzodiazepines, cognitive impairment and dementia**

The effectiveness and relative safety of benzodiazepines (BDZ), combined with the high prevalence of anxiety and sleep problems, have contributed to the extensive and perhaps excessive use of BDZ. The dispensing of BDZ rises with increasing age, from 20\% among those aged 65–69 years to 30\% in people over the age of 85 (Tu \textit{et al}., 2001), with approximately 17\% of those aged 75 years or more being chronic users (Jorm \textit{et al}., 1999). BDZ consumption in later life has been associated with hip fractures, motor vehicle accidents, suicide and increased mortality (Vinkers \textit{et al}., 2003).
BDZ and acute cognitive effects
Acute use of BDZ is associated with increased sedation, decreased attention, impaired motor coordination, increased reaction time and anterograde amnesia (impaired ability to learn new information) (Buffett-Jerrott and Stewart, 2002; Hanlon et al., 1998; Scharf et al., 1984). BDZ use was associated with increased incidence of memory problems over a 3-year period among 2765 older adults. However, the long-term cognitive consequences of BDZ consumption are less clear.

BDZ and long-term cognitive consequences
The Kungsholmen study was the first to examine this issue prospectively (Fastbom et al., 1998). People using BDZ at baseline and again after 3 years were reported to be less likely to have dementia (OR = 0.33, 95% CI = 0.12–0.82). It is unclear, however, whether these findings could be better explained by recall bias (subjects with dementia would be less likely to accurately recall the medications they were receiving), prescription bias (doctors might be less inclined to prescribe a benzodiazepine to an older person with cognitive impairment), selection bias (it is unclear how many ex-benzodiazepine users were included in the group of “nonusers”) or survivorship bias (people receiving BDZ for 3 years who were available for follow-up were significantly healthier than those who dropped out).

A more carefully designed, nested case–control study of a representative sample of 3669 older persons (aged 65 years or over) who were followed from 1989 to 1997 found that 150 subjects of the original sample developed dementia at follow-up. Older adults who had ever used BDZ were 1.7 (95% CI = 1.2–2.4) times more likely to develop dementia, whereas those who had regularly used BDZ in the past, but not at present, were 2.3 (95% CI = 1.2–4.5) more likely to develop dementia (Lagnaoui et al.). These findings are consistent with those of other prospective studies showing that long-term benzodiazepine use is associated with cognitive decline in later life (Paterniti et al., 2002).

Cannabis use, cognitive impairment and dementia
The cognitive consequences of regular cannabis use have not been as thoroughly investigated. Hart et al. (2001) assessed the acute cognitive effects of cannabis use in 18 young adults (mean age 25.1 years). Premature responses and the total time required to complete the tasks increased with increasing concentrations of tetrahydrocannabinol, the major psychoactive component of cannabis, but response accuracy was not affected. However, a control group was not used so firm conclusions cannot be drawn. The Epidemiologic Catchment Area study in Baltimore followed up 1318 participants aged 65 years and over for
12 years, with cognitive abilities being monitored with the MMSE (Lyketsons et al., 1999). There were no significant differences in cognitive decline between older adults who had been heavy users, light users and non-users of cannabis. However, the MMSE is not particularly sensitive to change over time in people without cognitive impairment, and this represents a significant limitation of this study.

Pope et al. (2001) reported the results of a methodologically more robust study, comparing the cognitive performance of heavy cannabis users, former heavy users and controls. Memory scores of current users were consistently lower than those of controls, although such a difference only reached statistical significance in one of the four scheduled assessments. Similarly, Solowij et al. (2002) reported the results of a cross-sectional study of 102 near-daily users, 51 short-term users and 33 non-users on nine cognitive tests assessing attention, memory and executive functions. Long-term users showed impaired learning, retention and retrieval when compared to controls, with cognitive performance being inversely correlated with the duration of cannabis use.

Heavy cannabis users are also more likely to make use of other drugs that have potentially detrimental effects on cognition, which may significantly confound the results of such investigations. Nevertheless, although current evidence is not sufficient to state definitively whether or not prolonged heavy cannabis use is associated with cognitive decline, most of the recent data are consistent with this hypothesis (e.g. Pope et al., 2003).

**Other drugs and cognitive function**

Several legal and illegal drugs are thought to affect cognitive function but their potential contribution to the development of dementia is unclear. For example, coffee consumption has been associated with better cognitive performance among older women (Johnson-Kozlow et al., 2002), and a recent small case–control study from Portugal found that patients with AD consumed significantly less caffeine prior to the diagnosis than controls (Maia and de Mendonca, 2002).

Certain psychopharmacological agents, such as antipsychotics and antidepressants, may also affect cognitive function, but there is no evidence to date that they increase the risk of dementia. Anti-inflammatory drugs, statins and medications to treat diabetes and hypertension might reduce the risk of dementia in later life, but data about such associations remain sparse and difficult to interpret (Lautenschlager et al., 2003). Until recently, hormone replacement therapy (HRT) was thought to potentially decrease the risk of dementia among post-menopausal women, but the results of the one suitably powered randomized trial, the Women’s Health Initiative Memory Study, showed that older women
treated with hormones were at increased risk of strokes and dementia (including AD) after a follow-up period of 4–5 years (Almeida and Flicker, 2005). Hence, clinicians need to be mindful of those findings when prescribing HRT to older postmenopausal women.

Finally, there is evidence that the chronic use of heroin and other illegal drugs impairs cognitive function (Gouzoulis-Mayfrank et al., 2000; Ornstein et al., 2000) and may lead to irreversible brain damage. However, data linking these agents to the development of dementia are currently not available.

**Conclusion**

What are the most frequent causes of dementia? The typical answer to this question would include a list of well-known conditions such as AD (approximately 50% of all cases), VaD (10–20%), frontotemporal dementia (5–10%) and dementia with Lewy bodies (10–15%). We would argue, however, that such a traditional reply contributes to obscure rather than reveal the true causes of dementia. Vascular disease, for example, does not necessarily cause dementia – strokes do! And what causes strokes? Well, the list is long, but would certainly include factors such as increasing age, high blood pressure, smoking, alcohol abuse, hyperlipidemia and sedentary lifestyle. Is smoking (or alcohol abuse) a cause of dementia, then? Certainly! However, as is the case for many of the proposed etiological factors of dementia, the relationship between drug use and cognitive impairment is neither direct nor simple. For this reason, it is probably unhelpful to ask how many cases of dementia are caused by alcohol abuse and smoking, or whether alcohol/smoking/drug-related dementia exist *per se*. It is more important, in our view, to appreciate that alcohol, smoking and perhaps other drug abuse can make a significant contribution to the causal pathway that ultimately leads to cognitive decline and impairment. In addition, the relationship between dementia and alcohol use is complex, with mild to moderate alcohol use probably being protective and heavy alcohol use causal. As such, they may prove to be important useful targets for interventions designed to decrease the burden of dementia in both developed and developing countries around the world.

**Conflict of interest**

None.

**Description of author’s roles**

All of the authors contributed to the review of the literature. G. K. Hulse and O. P. Almeida drafted the original version of the manuscript with the assistance of R. Tait and N. T. Lautenschlager.
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