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Moderate alcohol consumption and risk of developing dementia in the elderly:
The contribution of prospective studies

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Abstract

Moderate alcohol consumption, after controlling for potential confounding factors, has been found to be associated with a lower risk of developing dementia in several prospective epidemiological studies from Europe, the United States, and China. When analysing the type of alcoholic beverage consumed, moderate wine intake has been systematically associated with lower risk. However, moderate consumption has very different definitions across studies, ranging from monthly or weekly drinking to 3-4 drinks per day. In addition, different results have been observed according to sex: some studies found the same effect in men and women, while others found either no association or a stronger association in women. All of these results lead to the conclusion that the observed association is fragile and needs further confirmation.

Key words: alcohol drinking, dementia, Alzheimer Disease

Abbreviations:

PAQUID = Personnes Agees QUID

RR = risk ratio

Apo E4 = apolipoprotein E4 allele

HR = hazard ratio

Dementia is the most common disorder affecting the brain in older people.

Epidemiological studies have reported several risk factors and a consensus has emerged that sex, education, dietary, and vascular factors are likely to be important. Among dietary factors, alcohol consumption was found to be associated with a lower risk for dementia in some studies. We shall review several prospective studies on this topic.

The first prospective study to explore alcohol intake was the PAQUID program (1). A sample of 3,777 subjects aged 65 years or older was followed for 3 years and 99 incident cases of dementia were diagnosed. Alcohol consumption data were collected at baseline, with wine the main type of alcohol consumed, usually on a daily basis. Four categories of individuals were defined: non-drinkers, mild drinkers (consuming 1 or 2 drinks per day), moderate drinkers (consuming 3 or 4 drinks per day) and heavy drinkers (consuming more than 4 drinks per day). Lower risks of developing dementia were found among drinkers compared with non-drinkers, but the relationship was significant only for moderate drinkers (mild drinkers: risk ratio [RR]=0.81; moderate drinkers: RR=0.19; heavy drinkers: RR=0.31). No modification effect was found according to sex and the association did not change after adjusting for age, sex, education, occupation, and baseline cognition.

The Rotterdam Study followed 5,395 subjects aged 55 years or older over a period of 6 years; 197 incident cases of dementia were diagnosed (2). The number of drinks of alcohol (beer, wine, fortified wine, or spirits) was collected at baseline and five categories of intake were studied: no drinks consumed; less than 1 drink per week; more than 1 drink per week but less than 1 per day; 1 to 3 drinks per day; more than 3 drinks per day. The risk of developing dementia was lower among drinkers compared with non-drinkers (Table 1) and was significant in the 1-3 drinks per day category. The pattern was different in men and women. No association was found in women, whereas a lower risk was found for men drinking 1-3 drinks per day. A modification effect was found when the Apolipoprotein E4 allele (Apo E4)

was taken into consideration: the risk was lower among drinkers with an ApoE4 allele, whereas it was less clear for drinkers without the ApoE4 allele (Table 1). No difference was found according to beverage type, although beer tended to give marginally lower risk than wine.

In a prospective study of elderly people living in North Manhattan (3), 2,126 subjects were followed for 4 years and 260 incident cases of dementia were diagnosed. The number of drinks per week was collected at baseline and subjects were classified as non-drinkers, light drinkers (less than 1 drink per month to 6 drinks a week), moderate drinkers (1-3 drinks a day), and heavy drinkers (more than 3 drinks a day). Light and moderate categories were aggregated because of a low number of moderate drinkers. Indeed, in this sample, 70% of the subjects were non drinkers. When analysing the association between each alcoholic beverage type and dementia, wine was significantly associated with a lower risk among light to moderate drinkers (hazard ratio [HR]=0.64, p=0.018). When analysing the risk of Alzheimer's disease adjusted for age and sex, a decreased risk was observed in wine drinkers (HR=0.59, p=0.018) but the association became insignificant when education and the ApoE4 genotype (HR=0.69, p=0.11) were included. The risk ratios were greater than 1 for light to moderate beer or spirits drinkers (beer: HR=1.39, p=0.094, spirits: HR=1.34, p=0.152). When wine, beer and spirits were analysed simultaneously with full adjustment, the risk for Alzheimer's disease was lower in wine drinkers (HR=0.55, p=0.015), but higher for beer (HR=1.47, p=0.065) or spirits (HR=1.51, p=0.062) drinkers. A modification effect was found with the ApoE4 genotype. A significantly lower risk of dementia was found in light to moderate wine drinkers without an ApoE4 allele (HR=0.44, p=0.004) compared with non-drinkers, whereas the association disappeared for ApoE4 allele bearers (HR=1.10, p=0.093). No modification effect by sex was found.

The association between alcohol intake and risk for dementia was also examined in studies originally designed to explore cardiovascular events. During follow up, cognitive functioning was explored and nested case-control studies were performed. In the Copenhagen City Heart study (4), a nested case-control included 83 cases of dementia and 1,626 controls. Alcohol intake was collected in two ways: the number of drinks per week (less than 1, 1-7, 8-14, 15-21, 22 or more) and the frequency of intake (never / hardly ever, monthly, weekly, daily). No association was found between the number of drinks of alcohol consumed per week and the risk of dementia. When beer, wine and spirits intake were analysed simultaneously, a reduced risk was observed only for wine drinkers (monthly: HR=0.43 [0.23-0.82]; weekly: HR=0.33 [0.13-0.86]; daily: HR=0.57 [0.15-2.11]). Beer drinkers tended to have a higher risk (monthly: HR=2.28 [1.13-4.60]; weekly: HR=2.15 [0.98-4.78]; daily: HR=1.73 [0.75-3.99]) and no clear association was found in spirits drinkers (monthly: HR=0.81 [0.42-1.57]; weekly: HR=1.65 [0.74-3.69]; daily: HR=1.12 [0.43-2.92]). No difference was found between men and women.

Another nested case-control study was performed within the Cardiovascular Health Study, which included 373 cases of dementia and 373 controls (5). Levels of alcohol intake were defined as: 0 drinks per week; less than 1 drink per week; 1-6 drinks per week; 7-13 drinks per week; 14 or more drinks per week. The association between alcohol intake and the risk of dementia followed a J shaped curve, with a nadir for the category of 1-6 drinks per week (Table 2). The pattern was different for men and women: all drinker categories were associated with a lower risk in women, whereas a J-shaped curve was found for men (Table 2). A modification effect was observed by Apo E4: when the ApoE4 allele was absent, the risk was significantly lower among subjects who consumed 1-6 drinks per week. When the ApoE4 allele was present, the HR was below 1.00 only for light drinkers, and above 1.00 for heavier drinkers (Table 2). The odds of dementia were lower (although not significantly) for

wine drinkers (less than 1 drink per week: HR=0.72 [0.46-1.11]; 1-6 drinks per week: HR=0.72 [0.39-1.33]; more than 6 drinks per week: HR=0.62 [0.25-1.50]). However, the trend was not the same for beer (less than 1 drink per week: HR=0.84 [0.48-1.47]; 1-6 drinks per week: HR=0.74 [0.36-1.54]; more than 6 drinks per week: HR=1.96 [0.71-5.47]) or spirits drinkers (less than 1 drink per week: HR=0.84 [0.48-1.45]; 1-6 drinks per week: HR=1.17 [0.59-2.30]; more than 6 drinks per week: HR=1.08 [0.55-2.13]).

Several other prospective studies have reported an association between alcohol consumption and dementia. A Canadian study (6) reported that at least weekly consumption of alcohol was associated with a decreased risk of Alzheimer's disease (OR=0.68, [0.47-1.00]). In Sweden (7), the risk of dementia was estimated to be 0.5 [0.3-0.7] among light to moderate drinkers (1 to 21 drinks per week in men, 1 to 14 drinks per week in women). In China (8), light to moderate drinkers (1 to 21 drinks per week in men, 1 to 14 drinks per week in women) had a lower risk (RR=0.52 [0.32-0.85]) than non-drinkers, but a non-significant increased risk was observed in heavy drinkers (RR=1.45 [0.43-4.89]). A greater reduction of risk was observed for men (RR=0.37) than for women (RR=0.76).

All these studies tend to show the same result: light to moderate alcohol consumption is associated with a lower risk of developing dementia. Which mechanisms may be involved in the risk reduction of dementia? One possibility is that alcohol might act by reducing cardiovascular risk factors, either through an inhibitory effect of ethanol on platelet aggregation, or through the alteration of the serum lipid profile. A second possibility is that alcohol might have a direct effect on cognition through the release of acetylcholine in the hippocampus. Finally, another possible mechanism is through antioxidant activity of alcohol, particularly wine, which has been found to have important antioxidant effects.

However, the definition of light to moderate alcohol intake varies considerably across the studies reviewed. The classification of drinking as moderate ranges from monthly or

weekly drinking to 3-4 drinks per day, and many studies reported an association for an intake of less than 1 drink per day. As alcohol intake is self-reported, it is also expected to be under-reported. However, neither a linear dose-response nor a J-shaped curve were systematically found over all studies, and the association sometimes differed according to sex. The type of alcohol does not appear to be consistent across studies, yet wine intake is systematically associated with lower risk. If alcohol *per se* were associated with a decreased risk of developing dementia, the same pattern would be expected for beer and wine drinkers, yet beer has been found to be associated with higher risk in several studies.

When analysing these results and discrepancies, one can wonder about the nature of the association between alcohol consumption and the risk of dementia. It can be hypothesised that alcohol intake (especially light to moderate intake) is only a marker of a broader psychosocial behavior that is associated with a decreased risk of developing dementia. However, the analyses were controlled for many other risk factors and the association with alcohol was still significant. It is possible that important confounders (not yet identified) were not considered, which might explain some of the discrepancies between optimal intake, sex, or type of alcohol. Light to moderate wine drinkers may prove to be moderate with regard to other risk factors of dementia, and alcohol intake would only be an indicator of such behavior. Until such factors have been identified, we must be careful in how we interpret results relating to alcohol consumption. People should not be encouraged to drink more in the belief that this will protect them against dementia.

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Table 1: Hazard ratios of dementia according to alcohol consumption in the Rotterdam Study.

	No alcohol	<1 drink per week	≥1 per week but <1 per day	1-3 drinks per day	≥4 drinks per day
Total	1.00	0.82 (0.56-1.22)	0.75 (0.51-1.11)	0.58 (0.38-0.90)	1.0 (0.39-2.59)
Men	1.00	0.60 (0.27-1.34)	0.53 (0.28-1.0)	0.40 (0.21-0.74)	0.88 (0.32-2.44)
Women	1.00	0.91 (0.58-1.44)	0.91 (0.55-1.49)	0.85 (0.47-1.57)	-
ApoE4 absent	1.00	1.26 (0.67-2.37)	1.39 (0.73-2.64)	0.67 (0.31-1.46)	-
ApoE4 present	1.00	0.69 (0.35-1.34)	0.46 (0.23-0.94)	0.60 (0.30-1.21)	-

Table 2: Odds of incident dementia according to alcohol consumption (drinks per week) in the Cardiovascular Health Study

	None	<1	1-6	7-13	≥14
Total	1.00	0.65 (0.41-1.02)	0.46 (0.27-0.77)	0.69 (0.37-1.31)	1.22 (0.60-2.49)
Men	1.00	0.82 (0.38-1.78)	0.36 (0.17-0.77)	1.42 (0.58-3.48)	2.40 (0.86-6.64)
Women	1.00	0.52 (0.30-0.90)	0.57 (0.28-1.17)	0.23 (0.09-0.61)	0.39 (0.14-1.10)
ApoE4 absent	1.00	0.56 (0.33-0.97)	0.37 (0.20-0.67)	0.64 (0.30-1.38)	0.60 (0.24-1.51)
ApoE4 present	1.00	0.60 (0.24-1.52)	0.62 (0.21-1.81)	1.49 (0.33-6.65)	3.37 (0.67-17.1)