Moderate alcohol consumption and loss of cerebellar Purkinje cells

Pekka J Karhunen, Timo Erkinjuntti, Pekka Laippala

Abstract

Objective—To examine the dose-response effect of alcohol consumption on the number of cerebellar Purkinje cells.

Design—A prospective necropsy study combined with detailed reports on use of alcohol from a relative or friend. The number of Purkinje cells was counted in the anterior midsagittal section of the cerebellar vermis, the area of which was measured by computer assisted morphometry.

Setting—Department of forensic medicine, University of Helsinki.

Subjects—66 men, aged 35 to 69 years, subjected to medicolegal necropsy because of sudden or violent death. The average all year daily alcohol consumption over the year was 0 to 10 g in 17 men, 11 to 80 g in 24 men, and more than 80 g in 25 men.

Main outcome measures—Number of Purkinje cells, alcohol consumption.

Results—The numbers and density of Purkinje cells in the cross section of vermis showed a consistent but weak decrease with increasing daily alcohol intake but not with age. A wide variation in the cell counts was observed, especially in men drinking more than 80 g, suggesting differences in the susceptibility to effects of alcohol. Compared with men drinking 40 g or less, a long term moderate consumption of an average of 41 to 80 g daily was associated with a significant average loss of 242 (95% confidence interval 45 to 439) Purkinje cells (15.2%) from a mean of 1583 to 1341 cells. In those drinking 81 to 180 g the average loss was 535 (259 to 811) cells (33.4%) to a mean of 1048 cells. The density of cells in the cross section of vermis also fell significantly by 0.9 cell/mm (0.1 to 1.7) when the daily consumption exceeded 40 g and by 1.4 cell/mm (0.3 to 2.5) when the intake was 81 to 180 g. Only three cases (4.5%) in the series showed macroscopical cerebellar atrophy.

Conclusion—Long term intake of moderate doses of alcohol daily for 20-30 years may damage the cerebellum before the onset of macroscopical atrophy. Despite distinct individual differences an all year average daily alcohol intake of 41-80 g results in a risk of significant loss of Purkinje cells.

Introduction

Cerebellar atrophy is one of the main neurological manifestations related to alcohol abuse.¹⁻⁶ Neuropathologically, atrophic changes are localised particularly in the cerebellar vermis. The lesion is characterised by a decrease in the volume of molecular and granular layers, gliosis of the granular cell layer, and a decrease in the number of Purkinje cells.⁵ This leads to shrinkage of the anterior part of the vermis and loss of cerebellar weight.¹ Cerebellar atrophy is reported to occur in almost half of chronic alcoholics³ but may not be dose dependent.⁷ Only a few studies have reported brain damage related to moderate or social drinking. In

one neuropathological study moderate drinking was associated with a scanty decrease in brain weight and increase in ventricular volume.⁸ Another study that used computed tomography suggested that a high proportion of social heavy drinkers show brain atrophy.⁹ The effect of long term moderate use of alcohol on the human cerebellum is not well established.

We studied the effect of alcohol consumption on the number of Purkinje cells, the volume of the anterior vermis, and the occurrence of cerebellar atrophy. The study was conducted in a consecutive series of necropsies on men, comprising non-drinkers, moderate drinkers, and alcoholic heavy drinkers.

Subjects and methods

SUBJECTS

The original consecutive series comprised 104 men aged 35 to 69 years studied at the department of forensic medicine in Helsinki. The mean (SD; range) interval between death and necropsy was 3.2 (1.7; 1-7) days. The underlying causes of death were cardiovascular disease (51), accident or violence (19), intoxication (16), respiratory disease (8), other non-neoplastic disease (9), and neoplasms (1).

For 28 men there was no informant available for data on drinking habits or data were insufficient for calculating the daily dose; these men were excluded from the series. Of these, 21 had a history of alcoholism or excessive use of alcohol. Detailed data on the daily dose could thus be obtained for 76 (73%) of the cases. After exclusion of nine cases of acute cerebellar or cerebral laceration and/or haemorrhage and one of cerebral metastases, data on 66 of the 104 men (64%) were finally included.

ALCOHOL REPORTS

The spouse, a relative, or a close friend of the dead man was interviewed within two weeks after the death,¹⁰ and 14 different questions on his past and recent consumption of alcohol were asked. The intake of beer, wine, and spirits was asked about separately, and the amount of alcohol in the beverages was expressed as grams of absolute alcohol by using a catalogue supplied by the State Alcohol Monopoly (ALKO) of Finland. One bottle of beer (0.33 l) contained 9-15 g, wine 48-84 g (0.75 l), liquors 84-218 g (0.5 l), and spirits including whisky 140-160 g (0.5 l). If the trade name was not known, the average amount of alcohol in the beverage was used. The equivalent of 40 g of absolute alcohol is about 2 pints/1.13 l beer, 2 fl oz/440 ml wine, or 0.5 fl oz/112 ml spirits. The average all year daily alcohol dose was then determined by multiplying the daily dose by the number of drinking days and then dividing the result by 365. Based on this all year mean daily alcohol dose the 66 men of the series were divided into four groups (table 1): non-drinkers (0-10 g, n=17), low moderate drinkers (11-40 g, n=10), high moderate drinkers

Department of Public Health, University of Tampere, and Department of Forensic Medicine, University of Helsinki, Finland
Pekka J Karhunen, professor

Department of Neurology, Memory Research Unit, University of Helsinki, Finland
Timo Erkinjuntti, assistant professor

Department of Public Health, Biometry Unit, University of Tampere, Finland
Pekka Laippala, associate professor

Correspondence to:
Dr P J Karhunen,
Department of Public Health, University of Tampere, PL 607, SF-33101 Tampere, Finland.

BMJ 1994;308:1663-7

TABLE I—Age, body weight, and reported use of alcohol in medicolegal necropsy series of 66 men aged 35–69 years. Figures are means (SD) unless stated otherwise

Variable	All year daily alcohol dose (g)*				
	Non-drinkers (0-10)	Low moderate drinkers (11-40)	High moderate drinkers (41-80)	Heavy drinkers (81-180)	Alcoholic heavy drinkers (>180)
No of men	17	10	14	11	14
Age (years)	57.0 (9.9)	57.8 (10.0)	49.4 (9.7)	57.1 (8.3)	52.1 (9.2)
Body weight (kg)	76.7 (13.8)	83.2 (19.8)	70.5 (14.4)	74.0 (18)	74.0 (11)
Average all year daily use (g)	2 (2)	24 (9)	56 (23)	115 (39)	285 (82)
Duration of drinking history (years)	27.7 (10.1)	24.2 (12.9)	24.3 (12.1)	29.5 (10.8)	25.6 (10.2)
No of drinking days/year	35 (41)	155 (143)	221 (126)	333 (82)	332 (57)
Dose/drinking occasion (g)	30 (24)	120 (97)	141 (69)	145 (47)	333 (75)
No of men weekend drinking (dose > 80 g)	0	4	3	1	0
No of men binge drinking	0	2	5	0	5

*Cumulative annual alcohol intake divided by 365 days.

TABLE II—Validity of postmortem alcohol reports in medicolegal necropsy series of 66 men aged 35–69 years

Variable	All year daily alcohol dose (g)*				
	Non-drinkers (0-10)	Low moderate drinkers (11-40)	High moderate drinkers (41-80)	Heavy drinkers (>81-180)	Alcoholic heavy drinkers (>180)
No of men	17	10	14	11	14
Mean (SD) liver weight (g)	1737 (332)	1924 (325)	1942 (490)	1842 (601)	2284 (793)
Mean (SD) liver weight body weight (g/kg)	22.9 (3.2)	22.8 (3.5)	27.3 (3.6)	25.0 (6.4)	30.8 (9.3)
Fatty liver:					
Moderate degree	2	5	1	0	5
Severe degree	0	0	4	6	5
Bridging fibrosis	1	0	2	3	3
Alcoholic hepatitis	0	0	0	0	3
Liver cirrhosis	0	0	1	1	1
Chronic pancreatitis	0	0	1	1	2
Positive result on alcohol test	1	4	4	4	9

*Cumulative annual alcohol intake divided by 365 days.

(41–80 g, n=14), heavy drinkers (81–180 g, n=11), and alcoholic heavy drinkers (>180 g, n=14). The consumption pattern was defined as weekend drinking if the reported alcohol intake was centred on the time period from Friday to Sunday. Binge drinking was considered to consist of periods of uncontrolled drinking over several days to weeks, together with longer periods of no alcohol intake.

High moderate drinkers (41 to 80 g) were slightly younger than those with the lowest or highest reported consumption (table I). There was no correlation, however, between age and alcohol intake ($r=0.11$, 95% confidence interval -0.34 to 0.11). Body weight and over how many years a subject had drunk alcohol did not differ between the groups. No significant difference in alcohol dose per drinking occasion was observed between men drinking 41–80 g or 81–180 g. One third of the low or high moderate consumers (11 to 80 g) were weekend drinkers. Binge drinking was common among high moderate drinkers (41 to 80 g) and in alcoholic heavy drinkers (>180 g daily).

VALIDITY OF ALCOHOL REPORTS

The prevalence of alcohol related diseases of the liver and pancreas as well as positive blood alcohol tests was compared with reported alcohol consumption (table II). The validity of postmortem alcohol reports is indicated by increase in liver weight as well as occurrence of fatty liver, with a trend towards more severe fatty change in line with reported consumption. The same trend was observed in the occurrence of bridging fibrosis of the liver, alcoholic hepatitis, liver cirrhosis, and chronic pancreatitis, as well as in the prevalence of positive results to tests for alcohol carried out post-mortem.

PURKINJE CELLS

The cerebellum was weighed fresh and immersed in 10% buffered formalin. After fixation the left half of the cerebellum (sagittal cut) was photographed for morphological measurements and for visual assess-

ment of cerebellar atrophy. From the right half a 5 μ m section at the midline was used for microscopy.

The numbers of Purkinje cells were counted in the anterior vermis up to the central fissure (segment I)³ at a magnification of 40 $\times$ on sections stained with Luxol fast blue-cresyl violet.

MORPHOMETRIC MEASUREMENTS OF CEREBELLUM

The length (mm) and area (mm²) of the cross section of anterior vermis from the floor of the fourth ventricle to the central fissure were measured from the photographs by computer assisted morphometry, and the corresponding number of Purkinje cells/mm was calculated.

STATISTICAL EVALUATION

Confidence intervals were used to show significance between the average counts. To study the dependence between continuous variables Pearson's correlation coefficient with confidence intervals was calculated. The counts were also analysed by using multivariate regression analysis with square root transformation. Comparison of the means was carried out by using analysis of covariance with the age of the consumption group as a covariate. The pairwise comparisons were made by using the Bonferroni procedure. The computation was carried out on a VAX/VMS computer with BMDP statistical software (1993 version).

Results

ALCOHOL INTAKE AND PURKINJE CELLS

The numbers of Purkinje cells in the mid-sagittal section of the anterior cerebellar vermis tended to decrease dose dependently ($r=-0.34$; 95% confidence interval -0.54 to -0.11) with increasing all year average daily alcohol consumption (fig 1). A wide variation in the Purkinje cell counts was observed especially in men drinking more than 80 g. The number of cells did not correlate with the reported amount of alcohol consumed per drinking occasion ($r=-0.24$, -0.46 to 0.01) or with age ($r=-0.15$, -0.38 to 0.093) (fig 2). The multiple regression model with square root transformed number of Purkinje cells as dependent and the age and the alcohol intake as explanatory variables was fitted to the data. The model was significant with alcohol intake as a significant

FIG 1—Scatter diagram showing relation of Purkinje cell counts in anterior vermis to all year daily alcohol dose (cumulative annual intake divided by 365 days)

FIG 2—Correlation between age and Purkinje cell counts

explanatory variable (regression coefficient = -0.024, SE = 0.008; $P < 0.001$), but r squared was low (0.15). Accordingly, we modelled the data by comparing the means of successive subgroups defined by the level of alcohol consumption by using age as a covariate.

The mean number of Purkinje cells in the cross section of the vermis was similar in men who drank 10 g daily (mean (SD) 1573 (230) cells) and in low moderate consumers reported to have drunk 11 to 40 g daily (1600 (399)). Because there were no essential differences between the groups they were combined in statistical calculations to increase the power of analysis (table III). Compared with this group, intake of 41 to 80 g was associated with an average loss of 242 (15.2%) Purkinje cells (45 to 439) to a mean of 1341 cells. In those drinking 81 to 180 g the number of cells was decreased by an average of 535 (259 to 811) cells (33.4%) to a mean of 1048 cells. When the consumption exceeded 180 g no further decrease in the mean cell count was found.

In the analysis of the square root transformed cell counts age was found to be a significant covariate ($P = 0.05$) and the group means differed ($P = 0.0004$). When the age adjusted means of the groups were compared pairwise by using the Bonferroni procedure a significant difference was found between the combined group of the lowest consumption and high moderate (41-80 g) group ($P = 0.08$) (table III). When other groups were compared there was no further effect of alcohol on the cell counts because of wide variation in cell counts and fewer observations among heavy drinkers, although the magnitude of the difference between high moderate and heavy drinkers was almost as large.

ALCOHOL INTAKE AND DENSITY OF PURKINJE CELLS

In morphometric analysis a tendency for reduced length and area of the anterior vermis with the increase in alcohol intake was observed (table IV). The density of Purkinje cells in the cross section of the cerebellar vermis showed weak association with all year daily alcohol dose ($r = -0.27$, -0.48 to -0.033) but not with age ($r = -0.12$; -0.35 to 0.13). Compared with the group with the lowest reported alcohol intake (0 to

40 g) the density of Purkinje cells in the vermal surface decreased by 0.9 cell/mm (0.1 to 1.7 cells/mm) from a mean of 4.6 cells/mm to 3.70 cells/mm when the all year daily intake exceeded 40 g (table III). The decrease was 1.4 cell/mm (0.3 to 2.5 cell/mm) in the men drinking 81 to 180 g. No further decrease in cell density, however, was observed in men drinking more than 180 g. Age was again a significant covariate ($P = 0.007$). The observed difference in the age adjusted numbers of Purkinje cells/mm between the combined (0-40 g) and high moderate (41-80 g) group was significant (4.7 v 3.5 cells/mm, $P = 0.04$).

ALCOHOLIC LIVER DISEASE AND PURKINJE CELLS

The number of Purkinje cells tended to be lower in men with severe fatty liver ($n = 25$; 1239 (452) cells) compared with men without liver disease ($n = 35$; 1448 (359)). The number of patients with liver cirrhosis (three, 1165 (468)) or alcoholic hepatitis (three, 1381 (354)) was too small for statistical comparisons.

MACROSCOPIC CEREBELLAR ATROPHY

Brain weight and cerebellar weight tended to decrease with the increase of alcohol intake (table IV). No significant differences between the groups, were found, however.

Atrophic lesions, restricted to anterior and superior parts of the vermis, were observed in three cases, with a mean (SD) number of Purkinje cells of 614 (836). All cases were detected in men who consumed more than 80 g daily.

Discussion

Social consumption of moderate quantities of alcohol is the most common drinking pattern in Western countries.¹¹ Thus, attempts have been made to define a "safe dose" of alcohol.¹² Most of the studies delineating the adverse effects of alcohol are based on series of alcoholic or heavy drinkers, and effects of moderate alcohol consumption have not yet been well established. Moreover, most of the data available relate to liver injury.⁶

In our study moderate drinking was defined as an average all year daily use from 11 g to 80 g. Although all measures of alcohol intake obtained by interview methods suffer from uncertainty, our results suggest that long term moderate daily use of alcohol exceeding 40 g is associated with an increasing risk of loss of Purkinje cells in the cerebellar vermis. Cerebellar cell loss showed a great individual variation and did not increase in a dose dependent way when the all year daily intake exceeded 80 g. When we studied cell densities in the vermis an identical pattern emerged, which further supports the conclusions. Our results further suggest that an average all year daily dose from 41 g to 80 g of alcohol could be considered the threshold for neuronal damage induced by alcohol but that great individual variation in susceptibility to the effects of alcohol exists.

DOSE DEPENDENCE OF ALCOHOL INDUCED BRAIN DAMAGE

Recently it has been proposed that above a rather low but not precisely determined level of alcohol consumption the risk of liver cirrhosis is no further influenced by the amount of alcohol consumed.^{13,14} The effect of alcohol may thus be permissive rather than dose dependent, and additional factors must act before liver injury occurs.

In a previous study ataxic alcoholics were characterised by 24% lower annual consumption of alcohol and 33% lower maximum daily intake compared with non-ataxic alcoholics.⁷ This study suggested that alcoholic cerebellar degeneration may not be dose dependent and might be explained by idiosyncratic

TABLE III—Relation between reported use of alcohol, Purkinje cell counts, and density in medicolegal necropsy series of 66 men

Variable	All year daily alcohol dose (g)*			
	Non-drinkers or low moderate drinkers (0-40)	High moderate drinkers (41-80)	Heavy drinkers Heavy drinkers (81-180)	Alcoholic heavy drinkers (>180)
No of men	27	14	11	14
Mean (SD) No of Purkinje cells	1583 (296)	1341 (294)	1048 (540)	1158 (505)
Age adjusted square root transformed No of cells	40.1	35.6	31.2	30.1
Range of No of cells	1098-2093	785-1722	117-1643	147-1724
Mean (SD) No of Purkinje cells/mm	4.6 (1.3)	3.7 (0.8)	3.2 (1.8)	3.5 (1.5)
Age adjusted No of Purkinje cells/mm	4.7	3.5	3.3	3.4

*Cumulative annual alcohol intake divided by 365 days.

TABLE IV—Reported use of alcohol, main neuropathological findings, and morphometric measurements of cerebellum in medicolegal necropsy series of 66 men

Variable	All year daily alcohol dose (g)*				
	Non-drinkers (0-10)	Low moderate drinkers (11-40)	High moderate drinkers (41-80)	Heavy drinkers (81-180)	Alcoholic heavy drinkers (>180)
No of men	17	10	14	11	14
Brain weight (g)	1531 (173)	1491 (114)	1477 (103)	1456 (123)	1525 (158)
Cerebellar weight (g)	185 (19)	181 (13.3)	175 (15)	176 (20)	180 (18)
Cerebellar weight/body weight (g/kg)	2.55 (0.57)	2.24 (0.36)	2.70 (0.39)	2.45 (0.51)	2.44 (0.41)
Circumference of anterior vermis (mm)	367 (61)	342 (61)	367 (47)	331 (55)	359 (66)
Area of anterior vermis (mm ²)	406 (93)	348 (74)	374 (39)	353 (65)	363 (75)
Macroscopic cerebellar atrophy	0	0	0	1	2

*Cumulative annual alcohol intake divided by 365 days.

sensitivity to the neuronal effects of alcohol. Similarly, we could not find a linear dose dependent effect of alcohol. In another study, however, alcoholics with both clinical and radiological signs of atrophy were characterised by longer periods of heavy drinking compared with control alcoholics without such lesions.¹⁵

In concordance with previous studies^{5,16} we found only a weak association between liver damage and low Purkinje cell counts, suggesting that different mechanisms may operate in alcohol induced liver damage and in cerebellar atrophy.

MODERATE DRINKING

Except for our results and those of two other studies^{8,9} there are no reports on the effect of alcohol on the postmortem brain in moderate drinkers. Cala *et al* reported a high proportion (19/26) of unselected social heavy drinkers with cerebellar atrophy.⁹ Harper *et al* reported that brain weight and volumetric measurements indicated that moderate drinkers (by definition 20-80 g daily) seem to fit between the control and the medically uncomplicated alcoholic group.⁸ We found a slight but non-significant decrease related to alcohol in the mean weight of the brain and cerebellum. Thus, weight of the cerebellum does not reflect neuronal damage as sensitively as the loss of Purkinje cells.⁵ Moreover, the degree of tissue shrinkage of the cerebellum revealed by computed tomography⁵ or morphometry cannot be unequivocally equated with loss of Purkinje cells.

The occurrence of early neuronal damage in moderate and heavy drinkers with no macroscopical atrophy is indirectly further supported by other studies reporting a detectable effect of alcohol on cognitive tests in studies on twins,¹⁷ or neuropsychological impairment in alcoholics without radiological or clinical signs of cerebellar atrophy.¹⁸ In another study, however, no correlation between social drinking and cognitive functioning was found.¹⁹

The mechanism of alcohol induced cerebellar damage possibly involves hypoxia due to spasm of cerebral blood vessels,²⁰ fluidisation of membranes,²¹ focal accumulation of toxic aldehyde due to intraneural ethanol metabolism,²² or nutritional factors.⁶ Repeated traumas may also be a factor,¹⁸ as well as aging.³

PURKINJE CELL LOSS AS SENSITIVE MEASURE OF ALCOHOLIC INJURY

The earliest alcohol induced change is considered to be a decrease in the volume of granular and molecular layers,^{5,23} whereas a decrease in the number of Purkinje cells is observed later. We found a slight but non-significant decrease related to alcohol in the circumference and area of the anterior vermis, whereas the loss of Purkinje cells was more significant.

In previous necropsy series the prevalence of cerebellar atrophy varied from 1.7% to 4.1%,^{2,24} which is in line with our overall prevalence of 4.5%. In patients with a known history of alcoholism the prevalence of cerebellar atrophy was reported to be 26.8% to 37%.^{24,25} In our series only one of 10 men with an intake of more than 80 g had macroscopic cerebellar atrophy. This discrepancy may be explained by the fact that many of the most heavily drinking men were excluded from our series because of the lack of interview data. The difference could also be because our men were not attenders of clinics for alcoholics; they might be those heavy drinkers who are less susceptible to alcohol induced neuronal damage and thus do not reach clinics. The 33% decrease in Purkinje cells in the men who drank more than 80 g daily, however, is closely in line with figures from two previous necropsy studies that showed a significant 21-36% loss of Purkinje cells in the anterior vermis compared with controls.^{5,24}

Clinical implications

- Cerebellar atrophy is an important neurological manifestation of alcohol abuse
- Attempts have been made to set "safe" limits for alcohol consumption
- In a necropsy study loss of Purkinje cells was related to long term moderate daily intake of alcohol (41-80 g)
- Cell loss was greater in subjects who drank 81-180 g daily, but when consumption exceeded 180 g no further decrease in cell numbers was seen
- Long term moderate drinking may have detrimental effects on tasks such as driving that require proper cerebellar function

The self reports of alcoholics have been considered an unreliable measure of ongoing drinking,^{26,27} and more alcoholics may be "hidden" among the moderate drinkers than the teetotallers. In our study we used alcohol reports given by relatives or friends.¹⁰ In some settings such people seem to offer a more reliable assessment when compared with alcoholics' self-reports.^{26,27} There are several studies, however, in which relatives have estimated less than the drinkers themselves.²⁸ The average daily consumption at which risk of cerebellar damage begins might therefore be slightly over 40 g per day.

Our study shows that moderate long term intake of alcohol for 20-30 years may cause cerebellar damage. The results suggest a permissive rather than a dose related effect of alcohol on the cerebellum. Alcoholics without clinical or radiological signs of cerebellar atrophy have been found to be inferior to the reference population in neuropsychological tests of general intelligence and tests of short term memory.¹⁸ Thus, further studies are indicated to establish the extent that tasks requiring proper cerebellar function, such as driving, are compromised after long term moderate drinking as well as to explain genetic or acquired factors related to susceptibility to cerebellar injury induced by alcohol.

We thank Dr Kimmo Liesto, Dr Antti Männikkö, and Professor Antti Penttilä, who assisted with the interview data; Mrs Marjatta Puhakka for organising the interviews; Mr Seppo Tyynelä and Ms Hilikka-Liisa Vuorikivi for technical assistance; and Ms Tarja Ruotsalainen and Mrs Seija Kivimäki for secretarial assistance. PJK received support from the Yrjö Jahnsson Foundation and the Finnish Foundation for Alcohol Studies. TE is supported by the Paavo Nurmi Foundation.

1 Victor M, Adams R, Mancall EL. A restricted form of cerebellar cortical degeneration occurring in alcoholic patients. *Arch Neurol* 1959;1:579-688.

2 Victor M, Laureno R. Neurologic complications of alcohol abuse: epidemiologic aspects. In: Schoenberg BS, ed. *Advances in neurology*. 19th ed. New York: Raven Press, 1978.

3 Torvik A, Torp S. The prevalence of alcoholic cerebellar atrophy. A morphometric and histological study of an autopsy material. *J Neurol Sci* 1986;75:43-51.

4 Harper C, Kril J, Daly J. Are we drinking our neurones away? *BMJ* 1987;294:534-6.

5 Phillips SC, Harper CG, Kril J. A quantitative histological study of the cerebellar vermis in alcoholic patients. *Brain* 1987;110:301-14.

6 Thomson AD, Pratt OE, Jeyasingham M, Shaw GK. Alcohol and brain damage. *Hum Toxicol* 1988;7:455-63.

7 Estrin WJ. Alcoholic cerebellar degeneration is not a dose-dependent phenomenon. *Alcoholism, Clinical and Experimental Research* 1987;11:372-5.

8 Harper C, Kril J, Daly J. Does a "moderate" alcohol intake damage the brain? *J Neurol Neurosurg Psychiatry* 1988;51:909-13.

9 Cala LA, Jones B, Mastaglia FL, Wiley B. Brain atrophy and intellectual impairment of heavy drinkers: a clinical, psychometric computerized tomographic study. *Aust N Z J Med* 1978;8:147-53.

10 Karhunen PJ, Penttilä A. Validity of post-mortem alcohol reports. *Alcohol Alcohol* 1990;25:25-32.

11 Savolainen V, Penttilä A, Karhunen PJ. Delayed increases in liver cirrhosis mortality and frequency of alcoholic liver cirrhosis following an increment and redistribution of alcohol consumption in Finland: evidence from

- mortality statistics and autopsy survey covering 8533 cases in 1986-1988. *Alcoholism, Clinical and Experimental Research* 1992;16:661-4.
- 12 Royal College of Physicians. *The medical consequences of alcohol abuse. A great and growing evil*. London: Tavistock, 1987:125.
 - 13 Sørensen TIA. Alcohol and liver injury: dose-related or permissive effect? *Liver* 1989;9:189-97.
 - 14 Savolainen VT, Liesto K, Männikkö A, Penttilä A, Karhunen PJ. Alcohol consumption and alcoholic liver disease—evidence of a threshold level of effects of alcohol. *Alcoholism, Clinical and Experimental Research* 1993;17:1112-7.
 - 15 Muuronen A, Bergman H, Hidmarsch T, Telakivi T. Influence of improved drinking habits on brain atrophy and cognitive performance in alcoholic patients: a 5-year follow-up study. *Alcoholism, Clinical and Experimental Research* 1989;13:137-41.
 - 16 Acker W, Aps EJ, Majumbar SK, Shaw GK, Thompson AD. The relationship between brain and liver damage in chronic alcoholic patients. *J Neurol Neurosurg Psych* 1982;45:984-7.
 - 17 Gurling HM, Curtis D, Murray RM. Psychological deficit from excessive alcohol consumption: evidence from a co-twin control study. *Br J Addict* 1991;86:151-5.
 - 18 Hillborn M, Muuronen A, Holm L, Hindmarsch T. The clinical versus radiological diagnosis of alcoholic cerebellar degeneration. *J Neurol Sci* 1986;73:45-53.
 - 19 Alterman AI, Hall JG. Effects of social drinking and familial alcoholism risk on cognitive functioning: null findings. *Alcoholism, Clinical and Experimental Research* 1989;13:799-803.
 - 20 Altura BM, Altura BT, Gebrewold A. Alcohol-induced spasms of cerebral blood vessels: relation to cerebrovascular accidents and sudden death. *Science* 1983;220:331-3.
 - 21 Sun GY, Sun AY. Ethanol and membrane lipids. *Alcoholism, Clinical and Experimental Research* 1985;9:95-102.
 - 22 Kerr JT, Maxell DS, Crabb DW. Immunocytochemistry of alcohol dehydrogenase in the rat central nervous system. *Alcoholism, Clinical and Experimental Research* 1989;13:730-6.
 - 23 Tavares MA, Paula-Barbosa MM, Cadete-Leite A. Chronic alcohol consumption reduces the cortical layer volumes and the number of neurons of the rat cerebellar cortex. *Alcoholism, Clinical and Experimental Research* 1987;11:315-9.
 - 24 Torvik A, Lindboe CF, Rogde S. Brain lesions in alcoholics. A neuropathological study with clinical correlations. *J Neurol Sci* 1982;56:233-48.
 - 25 Skullerud K, Andersen SN, Lundevall J. Cerebral lesions and causes of death in male alcoholics. A forensic autopsy study. *International Journal of Legal Medicine* 1991;104:209-13.
 - 26 Watson CG, Tilleskjor C, Hoedecke-Schow EA, Pucel J, Jacobs L. Do alcoholics give valid self-reports? *J Stud Alcohol* 1984;45:344-8.
 - 27 Fuller RK, Lee KK, Gordis E. Validity of self-report in alcoholism research: results of a veterans administration cooperative study. *Alcoholism, Clinical and Experimental Research* 1988;12:201-5.
 - 28 Midanik LT. Perspectives on the validity of self-reported alcohol use. *Br J Addict* 1989;84:1419-23.

(Accepted 7 April 1994)

Risk of death from cancer and ischaemic heart disease in meat and non-meat eaters

Margaret Thorogood, Jim Mann, Paul Appleby, Klim McPherson

Abstract

Objective—To investigate the health consequences of a vegetarian diet by examining the 12 year mortality of non-meat eaters and meat eating controls.

Design—Prospective observational study in which members of the non-meat eating cohort were asked to nominate friends or relatives as controls.

Setting—United Kingdom.

Subjects—6115 non-meat eaters identified through the Vegetarian Society of the United Kingdom and the news media (mean (SD) age 38.7 (16.8) years) and 5015 controls who were meat eaters (39.3 (15.4) years).

Main outcome measures—Standardised mortality ratios for cancer, ischaemic heart disease, and total mortality in the two cohorts and death rate ratio in the non-meat eaters compared with meat eaters after adjustment for potentially confounding variables.

Results—Standardised mortality ratios (taking the value among the general population as 100) for ischaemic heart disease were 51 (95% confidence interval 38 to 66) for meat eaters and 28 (20 to 38) for non-meat eaters ($P < 0.01$). Values for all cancers were 80 (64 to 98) and 50 (39 to 62) for meat eaters and non-meat eaters respectively. After adjustment for the effects of smoking, body mass index, and socioeconomic status death rate ratios in non-meat eaters compared with meat eaters were 0.72 (0.47 to 1.10) for ischaemic heart disease and 0.61 (0.44 to 0.84) for all cancers.

Conclusions—The reduced mortality from cancer among those not eating meat is not explained by lifestyle related risk factors, which have a low prevalence among vegetarians. No firm conclusion can be made about deaths from ischaemic heart disease. These data do not justify advice to exclude meat from the diet since there are several attributes of a vegetarian diet apart from not eating meat which might reduce the risk.

Introduction

The diet of vegetarians differs from that of meat eaters in several respects other than the avoidance of meat. Vegetarians have a high intake of vegetables,

fruit, cereals, pulses, and nuts and their diet is therefore low in saturated fat and relatively high in unsaturated fats, carbohydrate, and non-starch polysaccharides (dietary fibre).¹ The micronutrient content of the diet also differs from that of meat eaters. Intake of several antioxidant nutrients is higher, while intakes of iron, zinc, and vitamin B12 are lower among vegetarians than meat eaters.² Several of the characteristics of a vegetarian diet have been shown to favourably influence cardiovascular risk factors^{1,3-5} and some have been associated in epidemiological studies with a reduced risk of ischaemic heart disease or certain cancers.^{6,7} Previous studies have reported lower mortality in vegetarians but they have used subjects who are members of religious or other groups or the data on confounding factors in the comparison group has been inadequate.⁸⁻¹⁰ Vegetarians tend to be thinner, smoke less, and are generally of higher socioeconomic status than the general population, all factors which are major determinants of total, cardiovascular, and cancer mortality. In an attempt to quantify any beneficial effects of a vegetarian diet and to determine the extent to which diet rather than lifestyle related risk factors determines the favourable mortality in vegetarians we studied mortality in about 6000 non-meat eaters and 5000 meat eating controls.

Subjects and methods

We recruited subjects between September 1980 and January 1984. Non-meat eaters were identified through advertisements in publications of the Vegetarian Society of the United Kingdom, the news media, and by word of mouth. Two of us (MT and JM) recruited subjects and no pressure was put on any members of the Vegetarian Society to participate. Of the 6115 non-meat eaters recruited 5728 were vegetarians (who did not eat meat or fish or ate these foods less than once a week, but did eat eggs or dairy products, or both) or vegans (who did not eat meat, fish, eggs, or dairy products) and 387 were fish eaters (who did not eat meat or ate meat less than once a week, may or may not have eaten eggs or dairy products, and ate fish at least once a week). A total of 2347 of the non-meat eaters were members of vegetarian or vegan societies, 24 were Seventh Day Adventists, and the

Department of Public Health and Policy, London School of Hygiene and Tropical Medicine, London WC1E 7HT
M Thorogood, senior research fellow
K McPherson, professor

Department of Human Nutrition, University of Otago, PO Box 56, Dunedin, New Zealand
J Mann, professor

Department of Public Health and Primary Care, University of Oxford, Oxford OX2 6HE
P Appleby, research officer

Correspondence to: Professor Mann.

BMJ 1994;308:1667-71