

# Effect of drinking on correlations between biochemical variables

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**SUMMARY** Several clinical laboratory tests correlate with alcohol consumption, for example, the plasma activities of gamma-glutamyl transpeptidase (GGT) and aspartate aminotransferase (AST), the concentrations of triglycerides (TG) and uric acid (UA) and the erythrocyte mean corpuscular volume (MCV). The correlations of these test results with each other have been studied in a population of men attending a multiphasic health-screening centre. The patterns of correlation were of two types: those between the pairs of variables GGT/TG, GGT/UA, TG/AST, and TG/UA were all unchanged as the level of alcohol consumption increased; the pairs of variables GGT/MCV, UA/AST, AST/MCV, UA/MCV, and GGT/AST all became more highly correlated as the level of alcohol consumption increased.

Several commonly performed tests reflect alcohol consumption in a normal, not overtly 'alcoholic' subject.<sup>1-3</sup> For example, high gamma-glutamyl transpeptidase activity, raised triglyceride or uric acid levels, or macrocytosis are each more likely to be found in a heavy drinker than in a light drinker or a non-drinker.<sup>4</sup> Each of these increased values might occur independently or might be correlated with each other; such correlations could be due in whole or in part to the effects of alcohol consumption. Correlations between gamma-glutamyl transpeptidase activity and triglyceride concentration<sup>5</sup> and between triglyceride and uric acid concentrations<sup>6</sup> have been reported.

Our approach has been to consider three possible models:

- (1) that the variables are completely uncorrelated;
- (2) that the variables are correlated, but the correlations are independent of admitted alcohol consumption; and
- (3) that the correlations vary with alcohol consumption;

and to test observed data against each of these models.

## Methods

### SUBJECTS

The subjects were 1918 apparently healthy men aged 17 to 78 with a median age of 46 years. The subjects were attending a multiphasic health-screening centre in Sydney where they answered an exten-

sive, computerised medical history questionnaire with some questions about alcohol consumption. A venepuncture yielded a heparinised plasma specimen for biochemical analysis and an EDTA blood specimen for haematological analysis.<sup>4</sup> Subjects were grouped on the basis of imputed alcohol intake: non-drinkers; those who claimed to drink less than 15 drinks per month, 15-45 drinks per month, 46-135 drinks per month, and more than 135 drinks per month. These drinking groups were arbitrarily assigned integer scores from zero for non-drinkers to four for the heaviest drinkers; this corresponds roughly to a logarithmic scale for admitted alcohol intake.

### BIOCHEMICAL TESTS

The tests carried out on the plasma, chosen because of their known association with alcohol consumption, were gamma-glutamyl transpeptidase activity (GGT) triglycerides (TG) and uric acid (UA) concentrations, aspartate aminotransferase activity (AST), and erythrocyte mean corpuscular volume (MCV).

### STATISTICAL METHODS

The distribution of each of these biochemical variables (except MCV) was skewed. To ensure approximate normality of these variables they were log transformed. (In fact results using the transformed variables were essentially identical with those obtained for the untransformed variables.) As correlations between untransformed variables are

likely to be more useful to the practising clinical biochemist only these correlations are presented here.

For each possible pair of variables, correlation coefficients, transformed to normality by Fisher's z-transformation<sup>7</sup> and weighted inversely by their known variances, were fitted to each of these statistical models which correspond to the biological models mentioned previously:

- (1) that the pair of variables is uncorrelated within each drinking group;
- (2) that correlations between the pair of variables exist and do not vary significantly between drinking groups; and
- (3) that correlations between the pair of variables exist and show a consistent trend over the drinking groups. This was done by fitting a linear regression of the transformed correlation coefficients with drinking groups.

The difference between the residual sum of squares of two models is chi-squared distributed if the models do not differ significantly. Furthermore, if the model is a good fit to the data, the residual sum of squares is also chi-squared distributed. In the analysis described here, the fits of all models were good. Models were fitted by weighted least squares using the computer program GLIM3.<sup>8</sup>

## Results

Correlations between the variables are given in the Table.

In non-drinkers, five of the 10 pairs of variables were significantly positively correlated, and one pair had a significant negative correlation, but in drinkers, the correlations were significant for all pairs. Partial correlations controlling for the effect of alcohol consumption were, in general, lower, and for two pairs, TG/MCV and UA/MCV, they were not significant.

The patterns of correlation between drinking groups differed between pairs of variables. For example, the correlation between GGT/AST is significant in non-drinkers and is larger in each successive heavier drinking group. Similarly, the correlations between the pairs GGT/MCV, UA/AST, and AST/MCV, although not significant in non-drinkers, were each significant in the whole drinking group, and the correlation for GGT/MCV was largest in the group with the highest reported alcohol consumption.

In addition, the correlation between UA/MCV, which was negative in non-drinkers, was positive and significant in drinkers overall. Of the 10 pairs of variables, there were significant effects of alcohol in five, which thus satisfied the third model outlined above. In a further four pairs, the correlation was significant and homogeneous over the five drinking groups. The remaining pair, TG/MCV, showed no significant correlation in any single group but was significant overall.

## Discussion

Different models proved to be appropriate for different pairs of variables; no single model was consistent with all of the observations. Firstly, when the entire group of drinkers was considered, the hypothesis that the variables were uncorrelated (model 1) was rejected in every case. It was, therefore, necessary to consider the nature of the correlations and the possible reasons for their existence.

Several pairs of variables had significant correlation coefficients, yet these correlation coefficients were independent of alcohol consumption, being present in the non-drinking group and persisting at about this same level through increasing alcohol intakes. These correlations were, therefore, best described by model 2. These pairs are GGT/TG, GGT/UA, TG/UA, and TG/AST, although the

Correlations between test results in the whole population studied and in subgroups classified by alcohol intake

	GGT/TG	GGT/UA	GGT/AST	GGT/MCV	TG/UA	TG/AST	TG/MCV	UA/AST	UA/MCV	AST/MCV
Non-drinkers (n=418)	0.27***	0.17***	0.24***	0.01NS	0.23***	0.18***	0.02NS	0.08NS	-0.10*	-0.08NS
All drinkers (n=1918)	0.30***	0.19***	0.59***	0.25***	0.28***	0.25***	0.09***	0.19***	0.11**	0.17***
All drinkers, partial correlations holding alcohol consumption constant (n=1918)	0.26***	0.13***	0.55***	0.14***	0.25***	0.21***	0.01NS	0.13***	0.01NS	0.06*
Drinking groups (drinks per month):										
less than 15 (n=421)	0.18***	0.03NS	0.36***	0.12**	0.21***	0.12**	-0.02NS	0.07NS	-0.06NS	0.07NS
15-45 (n=451)	0.30***	0.16***	0.40***	0.08*	0.18***	0.18***	0.04NS	0.14**	0.06NS	0.03NS
46-135 (n=417)	0.29**	0.18**	0.53***	0.19***	0.29***	0.12**	0.03NS	0.24***	-0.02NS	0.13**
over 135 (n=211)	0.31***	0.17***	0.64***	0.24***	0.33***	0.37***	-0.01NS	0.13*	0.07NS	0.10NS
Effect of drinking ( $X^2$ , see text)	1.12NS	0.70NS	47.5***	8.91**	2.27NS	2.42NS	0.00NS	4.24*	4.95*	7.20**

NS  $P > 0.05$ ; \* $0.01 < P < 0.05$ ; \*\* $0.001 < P < 0.01$ ; \*\*\*  $P < 0.001$ .

TG/AST correlation is higher in the heavier drinking group. This includes the group of tests for which other workers have reported correlations.<sup>5-6</sup> A definitive explanation for these correlations is not available. However, a possible explanation is that there are one or more environmental factors, some probably dietary, which produce these correlations through the induction of liver microsomal enzymes.<sup>5</sup> Meat consumption could be one such factor since some methods of cooking can produce meals which stimulate microsomal enzyme induction,<sup>9</sup> animal protein can affect lipid metabolism,<sup>10</sup> and the purine content of meat could also raise the plasma level of uric acid.

The third model, in which the correlations vary with alcohol consumption, fits best in two situations. For the pairs in which MCV is one variable, a significant positive correlation is found in the group of all drinkers. This correlation is reduced or eliminated by the partial correlation correcting for the effects of alcohol intake. Also the correlations are not significant (in one case negative) in the non-drinkers. It can reasonably be concluded that the correlations of MCV with the other variables are due to the dependence of each on alcohol intake.

Comparisons of the correlation coefficients and the partial correlation coefficients, using Fisher's z-transformation, showed that removing reported alcohol consumption significantly reduced the entire group's correlation coefficients between the pairs GGT/MCV ( $P < 0.001$ ), AST/MCV ( $P < 0.001$ ), UA/MCV ( $P < 0.001$ ), and TG/MCV ( $P < 0.02$ ). For the other pairs of variables, reported alcohol consumption did not significantly alter the correlations observed in the entire sample.

The other example of the third model is seen in the pair GGT/AST where the correlation increases progressively with increasing alcohol intake. In this case it seems probable that some physiological or pathological change occurs in some but not all subjects, which affects both of the variables, and that this change is more likely to occur the greater the alcohol intake. From our knowledge of these two enzymes, it is likely that this process is damage to liver cells caused by long-term alcohol abuse. However, it should be noted that GGT and AST are correlated at a highly significant level even in non-drinkers.

In conclusion, the variables GGT, AST, TG, and UA are associated in heavy drinkers. However, many of the comparisons between these variables

also show significant correlations in light drinkers and non-drinkers; the cause of these correlations remains speculative. For pairs including MCV (GGT/MCV, TG/MCV, UA/MCV, and AST/MCV), alcohol consumption accounts for a significant proportion of the correlation found in the general population. One interpretation of these results is that MCV is governed by a drinking-related process other than the one that affects GGT, TG, UA, and AST.

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