Serum Gamma-Glutamyl Transferase, Self-Reported Alcohol Drinking, and the Risk of Stroke

Pekka Jousilahti, MD, PhD; Daiva Rastenyte, MD, PhD; Jaakko Tuomilehto, MD, PhD

Background and Purpose—There is still conflicting evidence regarding a link between alcohol drinking and the risk of stroke. In most prospective studies, the assessment of the alcohol drinking has been based on self-reporting, which may be unreliable. The aim of the present study was to examine the relationship between stroke and both the self-reported alcohol drinking and the serum gamma-glutamyl transferase (GGT) concentration, which was regarded as a biological marker of alcohol drinking.

Methods—A prospective cohort study of 14 874 Finnish men and women aged 25 to 64 years who participated in a cardiovascular risk-factor survey in 1982 or 1987. The following risk factors, determined at baseline, were included in data analyses: self-reported alcohol drinking, GGT, smoking, blood pressure, serum cholesterol, and body mass index. The cohorts were followed until the end of 1994. Stroke events were identified through the national death registry and hospital discharge registry by computerized record linkage.

Results—Serum GGT concentration was associated with the risk of total and ischemic stroke in both genders. There was also a significant association among men between GGT and the risk of intracerebral hemorrhage and among women between GGT and the risk of subarachnoid hemorrhage. The relationships remained statistically significant also after adjustment for other risk factors. Self-reported alcohol drinking did not associate with any type of stroke.

Conclusions—These results support the hypothesis that excessive alcohol drinking is related to an increased risk of stroke. Biological markers of alcohol drinking, such as serum GGT level, are useful for the assessment of risks related to alcohol drinking. (Stroke. 2000;31:1851-1855.)

Key Words: alcohol drinking · gamma-glutamyltransferase · stroke
basis of the self-reported number of drinks consumed per week. The association between alcohol drinking and the risk of stroke was analyzed using alcohol both as continuous and as categorized dummy variable. The following amounts of alcoholic beverages were considered 1 drink: 33 cl beer, 16 cl wine, and 4 cl strong alcohol.

Based on the responses, the participants were classified into 3 smoking categories: current smokers, ex-smokers, and lifelong nonsmokers. In this study, the ex-smokers who had not smoked during the past 6 months were considered nonsmokers, and the ex-smokers who had gone without smoking during the past 6 months were considered smokers.

At the survey site, specially trained nurses measured height, weight, and blood pressure using the standardized protocol. Body mass index (BMI) (kg/m²) was used as a measure of relative body weight. Cholesterol and GGT were determined from fresh serum samples. Serum cholesterol was measured by an enzymatic method (CHOD-PAP, Boehringer Mannheim). GGT was measured by a kinetic method (Oy Medix Biochemica AB, Kauniainen, Finland), based on the recommendation of European Committee for Clinical Laboratory Standards. All samples were analyzed in the same central laboratory at the National Public Health Institute.

Mortality data were obtained from the Central Statistical Office of Finland. Data on nonfatal cerebrovascular events were received from the national hospital discharge register. Mortality data and hospital discharge register data were linked to the risk factor survey were excluded from the present analyses. The follow-up of each subject in our present analyses continued through the end of 1994, or until the time of the event between 1972 and the risk factor survey were excluded from the present analyses. The follow-up 154 896 person-years were accumulated. The number of acute cerebrovascular events during the follow-up was 261 among men and 209 among women.

Analysis of variance was used to study the association of serum GGT level with smoking, serum cholesterol, blood pressure, and BMI. Multivariate analyses were performed with the Cox proportional hazards model.¹⁴ The estimates of relative risks and their 95% confidence intervals were based on this model. In the analyses by the stroke subtype, those subjects who developed a stroke type other than the one analyzed were excluded. The statistical analyses were performed with the SAS statistical programs.¹⁵

## Results

Among both men and women there was a significant linear increasing trend in the mean levels of both systolic and diastolic blood pressures, serum total cholesterol, BMI, prevalence of smoking and self-reported alcohol drinking by quartiles of the serum GGT (Table 1).

Increasing serum GGT levels were associated with the increased risk of total stroke and ischemic stroke in both men and women. The risk ratios (logarithmic transformation of GGT) in men and women were 1.45 and 1.48 for total stroke and 1.51 and 1.59 for ischemic stroke, respectively (Table 2). Among men there was also a significant association (RR 2.08) between serum GGT and the risk of intracerebral hemorrhage. Among women a significant association (RR 1.91) between serum GGT level and the risk of intracerebral hemorrhage but not intracerebral hemorrhage. Among both men and women the risk ratios (logarithmic transformation of GGT) in men and women were 1.45 and 1.48 for total stroke and 1.51 and 1.59 for ischemic stroke, respectively (Table 2). Among men there was also a significant association (RR 2.08) between serum GGT and the risk of intracerebral hemorrhage. Among women a significant association (RR 1.91) between serum GGT and the risk of intracerebral hemorrhage but not intracerebral hemorrhage.

## Statistical Analyses

The relationship between serum GGT and stroke remained statistically significant also after adjustment for smoking, serum cholesterol, BMI, and systolic blood pressure. There was no linear association between the self-reported alcohol drinking and the risk of stroke (Table 2). When the

<table>
<thead>
<tr>
<th>TABLE 1. Age-Adjusted Risk Factor Levels in Men and Women Aged 25 to 64 Years, by Serum GGT Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk Factor</td>
</tr>
<tr>
<td>---------------------------------------------</td>
</tr>
<tr>
<td>Men (n=7176)</td>
</tr>
<tr>
<td>Smoking, %</td>
</tr>
<tr>
<td>Serum cholesterol, mmol/L</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
</tr>
<tr>
<td>Alcohol consumption, drinks/wk</td>
</tr>
<tr>
<td>GGT, U/L</td>
</tr>
<tr>
<td>---------------------------------------------</td>
</tr>
<tr>
<td>Women (n=7698)</td>
</tr>
<tr>
<td>Smoking, %</td>
</tr>
<tr>
<td>Serum cholesterol, mmol/L</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
</tr>
<tr>
<td>Alcohol consumption, drinks/wk</td>
</tr>
<tr>
<td>GGT, U/L</td>
</tr>
</tbody>
</table>
associated was analyzed with alcohol as a categorized dummy variable, there was a weak tendency for a J-shaped curve in women but not in men. The risk ratios of total stroke were 0.64 (95% CI 0.39 to 1.06), 0.93 (95% CI 0.49 to 1.80), and 1.22 (95% CI 0.57 to 2.64) in women who consumed 1 to 3 drinks/wk, 4 to 6 drinks/wk, and ≥7 more drinks/wk, respectively, as compared with the full abstainers (reference group, risk ratio 1.0). In men the cut points were 0, 1 to 5, 6 to 10, and >10 drinks/wk. The risk ratios were 1.0, 0.96 (95% CI 0.71 to 1.30), 0.94 (95% CI 0.65 to 1.37), and 0.96 (95% CI 0.67 to 1.40), respectively.

**Discussion**

In the present study the increase in serum GGT concentration, which was regarded as a biological marker of excessive alcohol drinking, was associated with the increased risk of ischemic stroke as well as of total strokes in both genders. A significant relationship was also found between serum GGT and hemorrhagic strokes, even though the results were inconsistent in men and women. This inconsistency may be due to the relatively small number of intracerebral and subarachnoid hemorrhages in the study cohort. On the other hand, the self-reported alcohol drinking was not significantly related to the risk of stroke, even though there was a mild tendency for a J-shaped curve in women. This is very likely due to underreporting and other biases common with self-reporting of alcohol use. Such an underreporting will result in a bias in estimating the association between alcohol drinking and the risk of stroke, which attenuates the true magnitude of the association.

The first study which showed that alcohol may be an independent risk factor for stroke was published in the late 1970s. A relationship between alcohol drinking and stroke was demonstrated in the first West Birmingham Stroke Project, which was a hospital-based study. Other studies have indicated an increased risk of stroke among recent heavy drinkers or binge drinkers. A J-shaped association has been postulated between alcohol drinking and ischemic stroke, whereas for intracerebral and subarachnoid hemorrhage a linear correlation with the amount of alcohol drinking has been detected. The association between alcohol drinking and the risk of stroke may be different in different populations. The relationship between alcohol and stroke was not confirmed in the community-based second West Birmingham Stroke Project. Several other studies also have failed to find any significant independent relationship between moderate drinking and risk of stroke.

There was a strong correlation between serum GGT and the known cardiovascular risk factors: the levels of all major risk factors increased with increasing GGT. Although a part of the association between serum GGT and the risk of stroke was mediated through these other risk factors, GGT remained a significant predictor of stroke also after adjustment for smoking, blood pressure, serum cholesterol, and BMI.

Alcohol is believed to increase the occurrence of a stroke mainly as a result of alcohol-induced hypertension. Clinical studies have also investigated the link between biochemical markers of alcohol drinking and blood pressure. Elevated levels of serum GGT activity have been associated with higher blood pressure levels. In the present study, the association between GGT level and the risk of stroke did not markedly change after adjustment for blood pressure. One possible explanation is that in addition to its long-lasting effect on blood pressure, alcohol has an acute hemodynamic effect. This effect cannot, however, be detected during the baseline measurements in a prospective study like ours, and therefore cannot be taken into account in the analyses.

It has been demonstrated that obesity and diabetes are associated with elevated serum liver enzyme activities and therefore may be denoted as a confounding factors, having an influence on determining the real role of alcohol on stroke development. It has also been shown that an acute stroke event is often followed by a transient rise in serum GGT.
level, which may affect the results in case-control studies but not in prospective cohort studies.

It has been postulated that alcohol may have an effect on the hemostatic system, which may predispose to different types of stroke. Nevertheless, these effects may either prevent or promote the occurrence of strokes, leaving the question about the true role of alcohol on stroke risk unanswered. In addition to its effect on blood pressure and the hemostatic system, alcohol drinking may predispose to cardiac arrhythmias and, further, to emboli formation and ischemic stroke. It is also possible that the association between alcohol drinking and the risk of stroke does not result from any direct biological effect of alcohol but instead may be mediated through the alcohol-related behavior. It has been suggested that nonpenetrating arterial trauma is a common cause of brain infarction, and traumas are commonly associated with excessive alcohol drinking and binge drinking.

Even though there is no optimal single laboratory marker for alcohol consumption, serum GGT level may reflect the usual alcohol drinking better than self-reporting. It has also been shown that GGT is more influenced by drinking intensity than drinking frequency. Thus, serum GGT level reflects an excessive alcohol drinking and might be a marker of heavy binge drinking. In the French population-based study, however, self-reported chronic alcohol drinking was associated with increased risk of stroke while GGT levels were not. These differences between studies may reflect ecological and cultural differences in alcohol drinking habits as well as in the accuracy of the reporting of alcohol drinking. The association between GGT and the risk of stroke may also be biased by chronic liver disease, which is much more common in France than in Finland.

In conclusion, the present study supports the hypothesis that excessive alcohol drinking increases the risk of stroke. Self-reporting of alcohol drinking, however, may be unreliable, and often underestimates the true risk. Thus, use of the biological markers of alcohol drinking, such as serum GGT, may be a helpful tool for risk assessment. A better understanding of the pathophysiological mechanism between alcohol drinking, biological markers, and the risk of stroke is an important issue for the primary prevention of stroke.

References


Serum Gamma-Glutamyl Transferase, Self-Reported Alcohol Drinking, and the Risk of Stroke
Pekka Jousilahti, Daiva Rastenyte and Jaakko Tuomilehto

Stroke. 2000;31:1851-1855
doi: 10.1161/01.STR.31.8.1851
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2000 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/31/8/1851

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/