RESEARCH REPORT

γ-Glutamyltransferase and risk of stroke: the EUROSTROKE project

M L Bots, J T Salonen, P C Elwood, Y Nikitin, A Freire de Concalves, D Inzitari, J Sivenius, A Trichopoulou, J Tuomilehto, P J Koudstaal, D E Grobbee

J Epidemiol Community Health 2002;**56**(Suppl I):i25–i29

See end of article for authors' affiliations

Correspondence to: Dr M L Bots, Julius Centre for Patient Oriented Research, Universtiy Medical Centre, Utrecht, room D01.335, Heidelberglaan 100, 3584 CX Utrecht, the Netherlands; M.L.Bots@jc.azu.nl

Accepted for publication 30 July 2001

Background: Alcohol consumption has been implicated in the aetiology of stroke. As data on alcohol consumption obtained by questionnaire are susceptible to missclassification, this study evaluated the assocation between γ-glutamyltransferase (γ-GT), as a marker for alcohol consumption, and fatal, non-fatal, haemorrhagic and ischaemic stroke in three European cohort studies, participating in EUROSTROKE.

Methods: EUROSTROKE is a collaborative project among ongoing European cohort studies on incidence and risk factors of stroke. EUROSTROKE is designed as a nested case-control study. For each stroke case, two controls were sampled. Strokes were classified according to MONICA criteria or reviewed by a panel of four neurologists. At present, data on stroke and γ-GT were available from cohorts in Cardiff (57 cases), Kuopio (66 cases), and Rotterdam (108 cases).

Results: An increase in γ-GT of one standard deviation (28.7 IU/ml) was associated with an age and sex adjusted 26% (95% CI 5 to 53) increase in risk of stroke. Adjustment for confounding variables such as drug use, history of myocardial infarction, total cholesterol, and diabetes mellitus did not materially attenuate the association. The risk of haemorrhagic stroke increased linearly with increase in γ-GT. The association for cerebral infarction was not graded: the risk increased beyond the first quartile, and remained increased. The association of γ-GT with stroke was significantly stronger among subjects without diabetes mellitus compared with subjects with diabetes mellitus (no association observed).

Conclusion: This EUROSTROKE analysis showed that an increased γ-GT, as a marker of alcohol consumption, is associated with increased risk of stroke, in particular haemorrhagic stroke.

A large number of observational studies have investigated the association between alcohol consumption and coronary heart disease. In general, results from these studies provide evidence of a reduced coronary heart disease risk with moderate alcohol consumption and that its beneficial effect is primarily attributable to alcohol irrespective of the type of drink.[1] Alcohol consumption has also been implicated in the aetiology of stroke. For haemorrhagic stroke an increase risk with increasing alcohol consumption has generally been reported.[2] For cerebral infarction, inverse and J shaped associations have been reported,[3–6] whereas in some studies no association was found. Data on alcohol consumption are generally based on questionnaire information. This approach may result in considerable missclassification of exposure status—that is, alcohol consumption. This misclassification may have resulted in biased estimates of the association between alcohol consumption and risk of stroke: a bias that, in general, attenuates (underestimates) the true magnitude of the association. It has been suggested that the serum level of γ-glytamyltransferase (γ-GT) may be used as an unbiased although not perfect marker for alcohol consumption.[7–9] In particular at high levels, it may reflect increased alcohol consumption, whereas at low levels non-alcohol related factors are the main determinants of alcohol consumption.

We set out to evaluate the association between γ-GT and haemorrhagic and ischaemic stroke using data from three European cohorts participating in EUROSTROKE.

METHODS

The rationale and design of EUROSTROKE have been described in detail elsewhere.[10] In short, EUROSTROKE is a collaborative study among European research centres to investigate (1) the variation in incidence of fatal and non-fatal ischaemic and haemorrhagic stroke among populations in different European countries; (2) whether the observed differences in stroke incidence across countries can be explained by differences in prevalence of established cardiovascular risk factors; (3) the relative importance of smoking and some selected dietary factors (potassium intake, alcohol consumption), haemostatic disturbances (fibrinogen) and comorbidity (rheumatic heart disease, atrial fibrillation) compared with established risk factors as determinants of the occurrence of ischaemic and haemorrhagic stroke. The EUROSTROKE database is drawn from ongoing European population-based prospective follow up studies (cohorts) and is designed as a case-control study nested within these ongoing studies. For each stroke case, two controls were sampled. Controls were matched on day of baseline examination only. Apart from its objectives, the EUROSTROKE database allows for aetiological analyses looking into various risk factors for stroke. EUROSTROKE formally started on 1 January 1994. At present, data on stroke and γ-GT from three cohorts were available for analysis.

Finland

The Finnish contribution to EUROSTROKE comes from the Kuopio Ischemic Heart Disease Risk Factor study, which is a population-based prospective cohort study comprised of an age stratified random sample of 2682 men aged of 42, 48, 54, and 60 years. The baseline examination was performed between 1984 and 1989.[11] Fatal and non-fatal stroke cases were collected through the national mortality statistics and

Abbreviations: γ-GT, γ-glutamyltransferase

the FINMONICA stroke registries. Stroke was defined according to FINMONICA criteria and definitions.[12] Case ascertainment from the baseline examination to 1 January 1993 revealed 74 stroke cases. Controls subjects (n=148) were randomly drawn from the cohort that remained free from stroke during follow up.

The Netherlands

The Dutch contribution to EUROSTROKE comes from the Rotterdam Study, which is a population-based prospective follow up study among 7983 subjects, aged 55 years or over, living in the suburb of Ommoord in Rotterdam, the Netherlands.[13] Baseline data were collected from March 1990 to July 1993. In the Rotterdam Study, information on incident fatal and non-fatal events is obtained from the general practitioners (GPs) working in the study district of Ommoord as described earlier.[14] The GPs involved report all possible cases of stroke to the Rotterdam research centre. Events are presented in coded information following the International Classification of Primary Care (ICPC).[15] With respect to the vital status of the participants, information is obtained at regular intervals from the municipal authorities in Rotterdam and also death of a participant is reported. When an event or death has been reported, additional information is obtained by interviewing the GP and scrutinising information from hospital discharge records in case of admittance or referral. All suspected cerebrovascular events reported by the GPs were submitted for review to the EUROSTROKE case review board. From baseline to 31 December 1994, 192 stroke cases were identified and submitted for review and a total of 384 control subjects were drawn from the remainder of the cohort that remained free from stroke during follow up. Altogether 157 events were classified as definite or probable strokes.

United Kingdom

The British contribution to EUROSTROKE comes from the Caerphilly Heart Disease study in Wales, United Kingdom, in which 2512 men, aged 45 to 59 years are participating.[16] Baseline examinations took place from 1979 to 1983. Follow up examinations were performed from 1984 to 1988 (phase II) and from 1989 to 1993 (phase III). Stroke events were registered through national mortality statistics, hospital discharge records, self report, and family report. Of the registered events, additional information on signs and symptoms, on neuroimaging, necropsy and a copy of the discharge records were collected. When complete, stroke cases were submitted for review to the EUROSTROKE case review board as described earlier. Recently, 100 stroke events had been submitted for review and 200 controls subjects had been drawn from the remaining cohort. Eighty four stroke cases were classified as definite/probable stroke by the EUROSTROKE review board.

EUROSTROKE case review board

The review board comprised of four Dutch neurologists. Based on all information, including symptoms and signs obtained by interviewing the GP or, in case of hospital referral, hospital data, the neurologists classified the events as definite, probable and possible stroke. Events were classified by two neurologists. In case of disagreement a third neurologist was consulted, whose opinion was decisive for the final classification. This analysis is restricted to definite and probable events. For this analysis an incident stroke was considered to have occurred when (1) the event had led to a hospitalisation and the hospital discharge record indicated a diagnosis of a new stroke. The clinical diagnosis was based on signs and symptoms, and neuroimaging investigations during hospital stay (definite stroke); or (2) in case of no hospitalisation, signs and symptoms associated with the event obtained from the GP records and interview were highly suggestive of a stroke according to the neurologists (probable stroke) or (3) in case of out hospital death, when the GPs reported that the cause of death was a cerebrovascular accident and a cardiac cause was judged by the GP to be highly unlikely (probable stroke).

The event was classified into first and recurrent stroke and into subarachnoid haemorrhage, intracranial haemorrhage, intracerebral infarction, and unspecified (not documented). For the non-MONICA centres (the Netherlands, United Kingdom) ischaemic stroke was further classified into lacunar infarct; total anterior circulation infarct; partial anterior circulation infarct; posterior circulation infarct and unspecified infarct (undocumented). The classification was made following the guidelines described by Bamford and coworkers[17] and by the European Atrial Fibrillation Trial.[18]

Cardiovascular risk factors

As EUROSTROKE is based on ongoing cohort studies, information on cardiovascular risk factors in each of the participating centres was already collected before the EUROSTROKE project was established. Whenever possible, an exhaustive attempt was made to further harmonise the collected information to make comparison across studies possible. Nevertheless, the baseline measurements could not be further standardised beyond the attempts done in each individual study.

In each of the centres information on smoking, alcohol consumption, and medical history, including current use of prescribed drugs, was obtained by questionnaire. The subject's smoking behaviour was categorised into current, former or never. Alcohol consumption was assessed by questionnaire in categories, never drinking, former drinker, current drinker and not current drinker (no distinction in never and former). Based on the available information in all cohorts, alcohol consumption was defined as current drinkers and non-current drinkers (former and never). In addition, an estimate of grams of alcohol per week was obtained. Presence of diabetes mellitus was generally based on the question "Do you suffer from diabetes mellitus?". In the Rotterdam study diabetes mellitus was considered present when subjects used blood sugar lowering drugs. Information on a history of stroke was obtained by direct questioning at baseline "Did you ever suffer from a stroke?". A similar approach was taken for myocardial infarction. Presence of angina pectoris was based on either the cardiovascular Rose questionnaire or direct questioning.

In general, systolic and diastolic blood pressure were measured twice at one occasion in sitting position. In Cardiff, only one blood pressure measurement was performed. Hypertension was considered present when the systolic blood pressure was 160 mm Hg or above, or, diastolic blood pressure was 95 mm Hg or above, or, current use blood pressure lowering drugs. Height and weight were measured and body mass index (kg/m^2) was calculated. In all four centres an electrocardiogram was made and the presence of a Q-wave myocardial infarction and left ventricular hypertrophy were assessed according to the Minnesota classification system, or in Rotterdam, by using the automated diagnostic classification system of the Modular Electrocardiogram Analysis System (MEANS).[19 20] Apart from Rotterdam, a fasting blood sample was taken for determination of serum lipids (total cholesterol, HDL cholesterol) and γ-GT.

Data analysis

The analyses were first performed for each centre separately. To identify potential confounding variables, cardiovascular risk factors were related to stroke using multivariate logistic regression models and to γ-GT using linear regression models. Factors that were related to both stroke and γ-GT ($p<0.10$), and that were not assumed to be in the causal pathway of γ-GT leading to stroke were considered confounding variables. Systolic blood pressure, diastolic blood pressure, hypertension,

Table 1 General characteristics of the study populations

Characteristic	Cardiff, UK	Kuopio, FIN	Rotterdam, NL	All
Case/control	57/124	66/134	108/321	231/579
Age (y)	59.9 (5.0)	55.0 (4.1)	73.6 (10.1)	65.9 (11.3)
Female (%)	*	*	64.6	34.1
Systolic pressure (mm Hg)	148 (23)	132 (17)	144 (24)	143 (23)
Diastolic pressure (mm Hg)	85.5 (12.7)	88.6 (10.4)	74.4 (13.2)	80.4 (14.0)
Total cholesterol (mmol/l)	5.8 (1.2)	6.1 (1.2)	6.6 (1.3)	6.3 (1.3)
HDL cholesterol (mmol/l)	1.01 (0.24)	1.27 (0.28)	1.33 (0.35)	1.27 (0.34)
Current smoking (%)	39.8	25.5	23.0	27.4
Body mass index (kg/m^2)	26.5 (3.5)	27.0 (3.5)	26.1 (3.6)	26.4 (3.6)
Diabetes mellitus (%)	4.4	7.0	8.4	7.1
History of MI (%)	8.8	13.0	13.9	12.5
History of stroke (%)	3.3	5.0	5.7	5.0
γ-GT (IU/ml)	32.8 (33.9)	29.9 (27.1)	29.3 (26.9)	30.2 (28.7)

Values are unadjusted proportions or means with standard deviations in parentheses of all subjects combined. *Only men participated in the study.

body mass index, current smoking, total and HDL cholesterol, history of stroke, history of myocardial infarction, diabetes mellitus and use of (any) drug were evaluated as potential confounders. γ-GT as predictor of stroke was studied as a continuous variable (per standard deviation 28.7 IU/ml) using logistic regression analysis. Initially, adjustments were made for age, sex, and subsequently for potential confounding cardiovascular risk factors.

An interaction term (γ-GT × centre) was used to study whether the association between level of γ-GT and stroke differed across the centres. Similarly, interaction terms for sex, age, drug use and diabetes mellitus were used to evaluate whether the associations differed between men and women, with age, across subjects with and without drug use and with and without diabetes mellitus. Results are presented as odds ratios, with their corresponding 95% confidence intervals (95% CI).

In the analyses in which information from all centres was combined (pooled analyses) γ-GT was studied as a continuous variable and in quartiles based on centre specific γ-GT distributions. Logistic regression analysis was applied (with three dummy variables) to evaluate the association between level of γ-GT and stroke. Adjustments were initially made for age, sex and subsequently for confounding factors. Separate analyses were performed for total stroke, first ever stroke, fatal stroke (death within 28 days after onset), non-fatal stroke, and for haemorrhagic stroke and cerebral infarction.

To evaluate whether increased γ-GT reflected increased alcohol consumption, we evaluated this association with Spearman correlation coefficients and linear regression models.

RESULTS

General characteristics of the studied populations are given in table 1. Characteristics of the events are presented in table 2. In the pooled analyses systolic blood pressure, diastolic blood pressure, hypertension, current smoking, history of diabetes mellitus, history of myocardial infarction and any drug use were positively and significantly related to total stroke. Male sex, systolic blood pressure, hypertension, total cholesterol, diabetes mellitus, history of myocardial infarction, and use of any drugs were positively and significantly related to γ-GT.

The statistical significance (p value) of interaction terms was 0.89 for centre, 0.41 for sex, 0.21 for age, and 0.63 for drug use. The p value of the interaction term for diabetes mellitus was 0.06, with the direction of the estimate indicating that the association of γ-GT and stroke was absent among subjects with diabetes mellitus (n=58) and present among those without diabetes mellitus. Results will therefore be presented for all subjects and for those without diabetes mellitus.

The association of γ-GT to stroke for each centre is given in figure 1. In all centres a positive association was seen without evidence for heterogeneity. The pooled analyses revealed an age and sex adjusted increased risk of stroke per standard deviation increase of 21% (95% CI 4 to 42) for all subjects and of 26% (95% 5 to 53) for subjects without diabetes mellitus. Additional adjustments for drug use, myocardial infarction, total cholesterol, and hypertension did not severely attenuated the findings (table 3).

Table 2 Stroke characteristics of the participating centres

Characteristic	Cardiff, UK	Kuopio, FIN	Rotterdam, NL	Pooled
Total stroke	57	66	108	231
Fatal	14	13	31	58
Non-fatal	43	53	77	173
Haemorrhagic	8	14	8	30
Ischaemic	40	48	62	150
Unspecified	9	4	38	51

Values are absolute numbers.

Results from analyses in quartiles of the γ-GT distribution showed that for haemorrhagic stroke a linear positive association was found, whereas for cerebral infraction no clear significant association was observed (fig 2).

In figure 3 the association of alcohol consumption in grams per week (in quartiles) with γ-GT is given. γ-GT was significantly increased in subjects with the highest alcohol intake. The Spearman correlation coefficients between alcohol intake (g/week) and γ-GT were significant and positive in every cohort (0.33 in Cardiff, 0.22 in Kuopio, 0.15 in Rotterdam).

DISCUSSION

This analysis from the EUROSTROKE project showed that an increased γ-GT is associated with an increased risk of stroke.

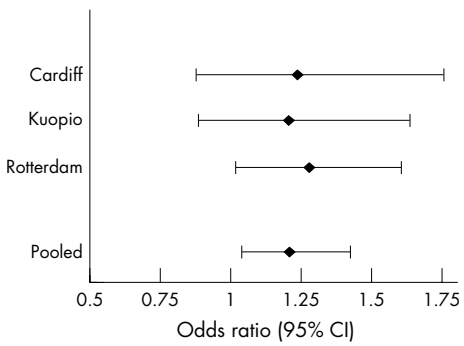

Figure 1 Risk of stroke per standard deviation increase in γ-GT, adjusted for age and sex, by centre. Subjects with diabetes mellitus excluded.

Table 3 Increase of γ-glutamyltransferase (per standard deviation) and risk of stroke

Stroke	Model I	Model II	Model III	Model IV
All	1.26 (1.05 to 1.53)	1.24 (1.02 to 1.49)	1.24 (1.02 to 1.52)	1.21 (1.00 to 1.49)
Fatal	1.70 (1.28 to 2.27)	1.69 (1.27 to 2.24)	1.84 (1.35 to 2.51)	1.77 (1.28 to 2.44)
Non-fatal	1.15 (0.92 to 1.44)	1.11 (0.88 to 1.39)	1.10 (0.87 to 1.39)	1.09 (0.86 to 1.38)
Haemorrhagic	1.75 (1.31 to 2.35)	1.71 (1.27 to 2.29)	1.80 (1.32 to 2.43)	1.70 (1.24 to 2.34)
Ischaemic	1.17 (0.93 to 1.48)	1.13 (0.90 to 1.43)	1.11 (0.87 to 1.41)	1.10 (0.86 to 1.40)
Ischaemic*	1.16 (0.93 to 1.45)	1.13 (0.90 to 1.41)	1.12 (0.89 to 1.41)	1.11 (0.88 to 1.40)

Values are odds ratios with 95% CI. Subjects with diabetes mellitus are excluded. *Ischaemic includes subjects with cerebral infarction and those with unspecified strokes. Model I Adjusted for age and sex; Model II Adjusted for age, sex, and drug use; Model III Adjusted for age, sex, drug use, myocardial infarction and total cholesterol; Model IV Adjusted for age, sex, drug use, myocardial infarction, total cholesterol and hypertension.

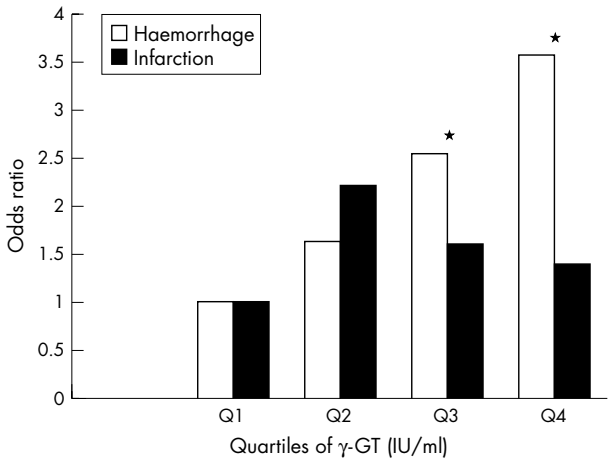

Figure 2 Risk of haemorrhagic and ischaemic stroke by quartile of the centre specific γ-GT distribution for all subjects are adjusted for age, sex, drug use, history of myocardial infarction, total cholesterol, and diabetes mellitus. Cut off points γ-GT: Cardiff, 17, 26, 41; Kuopio, 15, 21, 36; Rotterdam, 17, 22, 30. *p <0.05 compared with the first quartile.

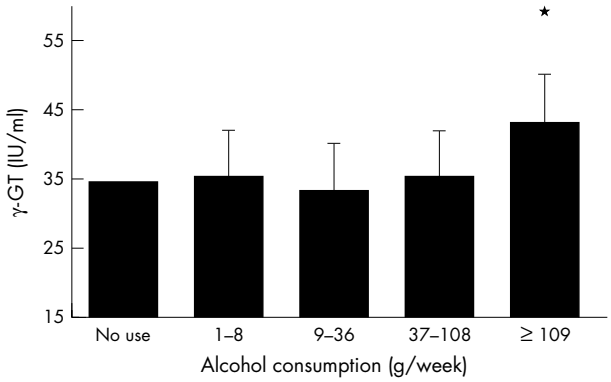

Figure 3 Relation of alcohol intake and γ-GT level. Results are adjusted for age and sex and are presented as means with 95% confidence limits. *p value <0.05.

The associations were independent of possible confounders—that is, hypertension, total cholesterol, drug use, and history of myocardial infarction. The association of γ-GT to stroke risk differed between subjects without diabetes mellitus (positive association) and those with diabetes mellitus (no association). A graded association between γ-GT and haemorrhagic stroke was found.

To appreciate these findings several aspects of this study should be considered. Firstly, EUROSTROKE is designed as a case-control study. The proportion of fatal cases across the centres differed from 19% in Kuopio to 28% in Rotterdam (table 2), the latter may be indicative for some underrepresentation of non-fatal cases, although a 28% case fatality is not particularly high. It is not likely that the completeness of non-fatal case ascertainment is differential across alcohol consumption status, although this cannot be verified. Secondly, as the number of haemorrhagic strokes is limited (n=30), these stroke type specific results should be interpreted with some caution. Strengths of this study include the fairly large number of well diagnosed and classified total stroke events for both men and women, presence of data on a large number of potential confounders, a wide age range, and the risk factor assessment before the occurrence of the stroke event.

Key points

- Moderate alcohol consumption reduces coronary heart disease risk, but how about stroke risk?
- γ-GT, as an unbiased marker for alcohol consumption, is associated with an increased risk for stroke.
- A graded association with haemorrhagic stroke was found.

An increased level of γ-GT has been suggested to be a reasonable marker of alcohol consumption. At lower levels of γ-GT, its main determinants were total cholesterol, drug use and presence of diabetes mellitus, whereas at high level, alcohol consumption is the main determinant.[9] Our results (fig 3) are in agreement with these findings. In these analyses we found no difference in the association of γ-GT and risk of stroke in subjects with or without current drug use. Adjustment for drug use and total cholesterol did not materially affect the magnitude of the associations. In contrast with subjects without diabetes mellitus, in diabetic patients (n=58) no evidence of an association of γ-GT to stroke was found. The sample size of this subgroup is very small, so that definite conclusion cannot be drawn from this analyses. However, the observation that subjects with diabetes mellitus have increased γ-GT levels compared with non-diabetics most probably reflects the use of drugs known to induce an γ-GT increase rather than increased consumption of alcohol.

The linear association between γ-GT and haemorrhagic stroke accords with the available evidence that shows a graded association between alcohol consumption and haemorrhagic stroke.[2] It is well documented that increased use of alcohol leads to an increase in blood pressure. The observation that additional adjustment for blood pressure did not severely affect the magnitude of association provides evidence that the association of γ-GT with haemorrhagic stroke is not entirely mediated through an increase in blood pressure.

In this study we observed no significant increased risk of γ-GT with cerebral infarction, which is in contrast with data that suggest inverse or J-shaped relations between alcohol consumption and cerebral infarction.[3–6] Even after adjustment for potential confounders is may be that the increased risk of stroke at lower γ-GT levels may reflect residual confounding, whereas the increased risk of stroke at the higher levels of γ-GT most probably reflects the effects of high alcohol intake rather than moderate alcohol intake.

In conclusion, we showed that an increased γ-GT in three European cohorts is associated with increased risk of stroke. The magnitude of the association is more pronounced for haemorrhagic stroke than for cerebral infarction.

ACKNOWLEDGEMENTS

Funding: EUROSTROKE is supported by grant BMH1-CT93–1786 from the European Community BIOMED I programme and by grant CIPD-CT94–0256 from the European Community PECO programme.

We acknowledge three Dutch neurologists, who in addition to one of us (P J Koudstaal) contributed to the classification of the stroke events: Jelis Boiten, University Hospital Maastricht, Maastricht; Jaap Kappelle, University Hospital Utrecht, Utrecht; and Martien Limburg, Academic Medical Centre, Amsterdam. We thank Oystein Kruger of the National Institute of Public Health, Community Medicine Research Unit in Verdal, Norway for his willingness to participate in EUROSTROKE.

Authors' affiliations

M L Bots, D E Grobbee , Epidemiology and Biostatistics, Erasmus University Medical School, Rotterdam, the Netherlands
M L Bots, D E Grobbee , Julius Center for Patient Oriented Research, University Medical Centre Utrecht, Utrecht, the Netherlands
J T Salonen, Research Institute of Public Health, University of Kuopio, Kuopio, Finland
P C Elwood, Centre for Applied Public Health Medicine, University of Wales College of Medicine, Cardiff, UK
Y Nikitin, Russian Academy of Medical Sciences Siberian Branch, Institute of Internal Medicine, Novosibirsk, Russia
A Freire de Concalves, Neurology, Hospitais da Universidade de Coimbra, Coimbra, Portugal
D Inzitari, Neurological and Psychiatric Sciences, University of Florence, Florence Italy
J Sivenius, Department of Neurology, Kuopio University Hospital, Kuopio, Finland
A Trichopoulou, Hygiene and Epidemiology, University of Athens Medical School, Athens, Greece
J Tuomilehto, Epidemiology and Health Promotion, National Public Health Institute, Helsinki, Finland
P J Koudstaal, Neurology, University Hospital Rotterdam Dijkzigt, Rotterdam, the Netherlands

REFERENCES

1 **Rimm EB**, Klatsky A, Grobbee DE, *et al*. Review of moderate alcohol consumtion and reduced risk of coronary heart disease: is the effect due to beer, wine or spirits?. *BMJ* 1996;**312**:731–6.
2 **Thrift AG**, Donnan GA, McNeil JJ. Epidemiology of intracerebral hemorrhage. *Epidemiol Rev* 1995;**17**:361–81.
3 **Camargo CA Jr**. Moderate alcohol consumption and stroke: the epidemiologic evidence. *Stroke* 1989;**20**:1611–26.
4 **Jamrozik K**, Broadhurst RJ, Anderson CS, *et al*. The role of lifestyle factors in the etiology of stroke. A population-based case-control study in Perth, Western Australia. *Stroke* 1994;**25**:51–9.
5 **Palmer AJ**, Flechter AE, Bulpitt CJ, *et al*. Alcohol intake and cardiovascular mortality in hypertensive patients. *J Hypertens* 1995;**13**:957–64.
6 **Hasagi H**, Romelsja A, Gerhardsson de Verdier M, *et al*. Alcohol consumption and stroke mortality. 20 year follow-up of 15,077 men and women. *Stroke* 1995;**26**:1768–73.
7 **Hoeskema HL**, de Bock GH. The value of laboratory tests for the screening and recognition of alcohol abuse in primary care patients. *J Fam Pract* 1993;**37**:268–73.
8 **Peck K**, Shinton R, Beevers G. Is serum gamma-glutamyl transferase a good marker for alcohol intake in stroke patients? *Postgrad Med J* 1990;**66**:710–13.
9 **Nilssen O**, Forde OH, Brenn T. The Tromso Study. Distribution and population determinants of gamm-glutamyl transferase. *Am J Epidemiol* 1990;**132**:318–26.
10 **Grobbee DE**, Koudstaal PJ, Bots ML, *et al*. Incidence and risk factors for ischaemic and haemorrhagic stroke in Europe. EUROSTROKE: A collaborative study among research centers in Europe: Rationale and design. *Neuroepidemiology* 1996;**15**:291–300.
11 **Salonen JT**, Salonen R, Seppänen K, *et al*. High density lipoprotein, HDL_2 and HDL_3 subfractions and the risk of acute myocardial infarction: a prospective population study in Eastern Finnish men. *Circulation* 1992;**84**:129–39.
12 **Tuomilehto J**, Sarti C, Narva EV, *et al*. The FinMonica stroke register. Community-based stroke registration and analysis of stroke incidence in Finland, 1983–1985. *Am J Epidemiol* 1992;**135**:1259–70.
13 **Hofman A**, Grobbee DE, Jong PTVM de, *et al*. Determinants of disease and disability in the elderly. The Rotterdam Elderly Study. *Eur J Epidemiol* 1991;**7**:403–22.
14 **Bots ML**, Hoes AW, Koudstaal PJ, *et al*. Common carotid intima-media thickness and risk of stroke and myocardial infarction. The Rotterdam Study. *Circulation* 1997;**96**:1432–7.
15 **Lamberts H**, Wood M, Hofmans-Okkes I. *The international classification of primary care in the European Community*. Oxford: Oxford University Press, 1991.
16 **Caerphilly and Speedwell collaborative heart disease studies**. The Caerphilly and Speedwell Collaborative Group. *J Epidemiol Community Health* 1984;**38**:259–62.
17 **Bamford J**, Sandercock P, Dennis M, *et al*. Classification and natural history of clinically identifiable subtypes of cerebral infarction. *Lancet* 1991;i:1521–6.
18 **European Atrial Fibrillation Trial Study Group**. Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. *Lancet* 1993;**342**:1255–62.
19 **Van Bemmel JH**, Kors JA, van Herpen G. Methodology for the Modular Electrocardiogram Analysis System (MEANS). *Methods Inf Med* 1990;**29**:346–53.
20 **Willems JL**, Abreu-Lima C, Arnaud P, *et al*. The diagnostic performance of computer programs for the interpretation of electrocardiograms. *N Engl J Med* 1991;**325**:1767–73.