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RESEARCH REPORT

Left ventricular hypertrophy and risk of fatal and non-fatal stroke. EUROSTROKE: a collaborative study among research centres in Europe

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Background: This study investigated the association between electrocardiographically assessed left ventricular hypertrophy (LVH) and fatal, non-fatal, haemorrhagic and ischaemic stroke in four European cohorts participating in EUROSTROKE.

Methods: EUROSTROKE is a collaborative project among ongoing European cohort studies to investigate differences in incidence of, and risk factors for, stroke between countries. 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. LVH was assessed according to the Minnesota code or the automated diagnostic MEANS classification system. For this analysis, data on LVH and stroke were available from cohorts in Cardiff (84 cases/200 controls), Kuopio (60/116), Rotterdam (114/334), and Novosibirsk (62/168). Results are adjusted for age and sex.

Results: LVH was associated with a twofold increased risk of stroke (odds ratio 2.1 (95% CI 1.3 to 3.5)). The risk was particularly pronounced for fatal stroke (4.0 (95% CI 2.1 to 7.9)), whereas the risk was non-significantly increased for non-fatal stroke (1.5 (95% CI 0.8 to 2.7)). The increased risk was more pronounced in smokers: for total stroke 3.5 (95% CI 1.5 to 8.1) versus 1.6 (95% CI 0.8 to 3.1) in non-smokers. Adjustment for systolic blood pressure and body mass index attenuated the associations. LVH was not preferentially associated with a particular type of stroke, although the association with cerebral infarction was stronger.

Conclusion: This analysis of the EUROSTROKE project indicates that LVH assessed by electrocardiogram is a predictor of stroke. The association seems to be stronger for fatal stroke than for non-fatal stroke and is more pronounced in smokers.

It has been convincingly shown that subjects with left ventricular hypertrophy (LVH) are at a considerable increased risk of coronary morbidity and mortality both among the general population^{1,2} and among hypertensive patients.^{3,4} Also, in subjects with recent cerebral ischaemia, LVH is a powerful predictor of future cardiac events.⁵ Furthermore, evidence is emerging that regression of LVH may reduce the risk of cardiovascular disease,⁶ which emphasises the importance of LVH assessment in risk profiling.⁷

In most studies on the association of LVH with future disease, cardiovascular disease included a variety of clinical manifestations, such as angina pectoris, myocardial infarction, congestive heart failure, sudden cardiac death, and occasionally stroke. A number of studies, however, have specifically investigated the association of LVH with stroke.⁸⁻¹⁴ These studies were either restricted to fatal stroke only, or no distinction between fatal and non-fatal stroke was made. Furthermore, differences in associations with various types of stroke have not been evaluated.

We evaluated the association between electrocardiographically assessed LVH and fatal, non-fatal, haemorrhagic and ischaemic stroke by combining data from four European cohorts participating in EUROSTROKE.

METHODS

The rationale and design of EUROSTROKE have been described in detail elsewhere.¹⁵ 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 from four cohorts were available for analysis.

EUROSTROKE case review board

Stroke was defined as a clinical event of rapid onset consisting of neurological deficit lasting more than 24 hours unless death supervenes, or if it lasts less than 24 hours, an appropriate lesion to explain the deficit is seen in a brain image. The event

Abbreviations: LVH, left ventricular hypertrophy

could not be directly caused by trauma to the brain, tumour, or infection. This definition included subjects presenting with signs and symptoms suggestive of a subarachnoid haemorrhage, an intracerebral haemorrhage, ischaemic cerebral infarction, and subjects with a transient ischaemic attack, provided neuroimaging has been performed. A case reviewing panel consisting of four neurologists classified stroke events occurring in EUROSTROKE based on the information that was obtainable such as patients history, results from a lumbar puncture, computed tomography or magnetic resonance images, findings from a necropsy report. Final codes from existing and operating registries, such as, for example, the FINMONICA registry were not reviewed separately, but used as coded. Based on the information present, the neurologist classified the event into first and recurrent stroke, and into subarachnoid haemorrhage, intracranial haemorrhage, intracerebral infarction, or unspecified stroke. In addition, the certainty of the diagnosis was assessed in definite, probable, possible, and no stroke. Events were classified by two neurologists; in case of disagreement a third arbitrated.

This analysis is restricted to definite and probable events. 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 general practitioner's records were highly suggestive of a stroke according to the neurologists (probable stroke) or (3) in case of out hospital death, when the general practitioner reported that the cause of death was a cerebrovascular accident and a cardiac cause was judged by the general practitioner to be highly unlikely (probable stroke).

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 42, 48, 54 and 60 years. The baseline examination was performed between 1984 and 1989.¹⁶ Fatal and non-fatal stroke cases were collected through the national mortality statistics and the FINMONICA stroke registries. Stroke was defined according to FINMONICA criteria and definitions.¹⁷ 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.¹⁸ 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.¹⁹ In short, 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).²⁰ 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

Key points

- Stroke is a major cause of morbidity and mortality.
- ECG LVH can be easily assessed.
- LVH predicts stroke.
- Association seems more prominent in smokers.

were submitted for review to the EUROSTROKE case review board. From baseline to 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.

Russia

The Russian contribution to EUROSTROKE originates from studies performed in the Octyabrsky, the Kirovsky and Leninsky districts of Novosibirsk, Siberia. The Novosibirsk cohort is based on three population-based surveys, which were conducted between 1984 and 1989 as part of the WHO MONICA project.²¹ The Novosibirsk cohort comprises 9006 men and women aged 25 to 64 years. Stroke cases were collected through a specifically developed stroke registry, aiming to identify fatal and non-fatal hospitalised and non-hospitalised stroke patients.^{22, 23} Stroke events were defined according to MONICA criteria and definitions.²⁴ From baseline to December 1995, a total of 100 stroke cases had been identified and 200 control subjects were drawn from the database. Finally, 79 subjects proved to be true 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.²⁵ 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 case review board.

Cardiovascular risk factors

Because EUROSTROKE is based on 10 ongoing cohort studies, information on cardiovascular risk factors in each of the participating centres was already collected before the formal start of the EUROSTROKE project. Whenever possible, an exhaustive attempt was made to further harmonise the collected information to make comparison across studies possible. Nevertheless, any 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 was obtained by questionnaire. The subject's smoking behaviour was categorised into current, former or never. Alcohol consumption was categorised into current drinkers and non-current drinkers (former and never). In addition, an estimate of grams of alcohol per day 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,

Table 1 General characteristics of the study population

Characteristic	Cardiff, UK	Kuopio, FIN	Rotterdam, NL	Novosibirsk, RUS	All
Case/control	84/200	60/116	114/334	62/168	320/808
Age at entry (y)	57.6 (5.9)	55.2 (4.1)	74.0 (10.1)	51.6 (9.1)	62.9 (13.0)
Female (%)	*	*	64.5	40.1	37.2
Systolic pressure (mm Hg)	146 (22)	132 (18)	144 (24)	145 (26)	143 (24)
Diastolic pressure (mm Hg)	86.2 (12.7)	88.7 (10.4)	74.2 (12.8)	93.4 (14.1)	83.6 (15.6)
Total cholesterol (mmol/l)	5.8 (1.2)	6.1 (1.2)	6.6 (1.3)	5.8 (1.3)	6.2 (1.3)
HDL cholesterol (mmol/l)	1.05 (0.33)	1.26 (0.28)	1.34 (0.37)	1.27 (0.38)	1.26 (0.37)
Current smoking (%)	47.1	27.9	22.7	35.1	31.2
Body mass index (kg/m ²)	26.6 (3.6)	26.9 (3.4)	26.1 (3.7)	28.3 (5.3)	26.9 (4.2)
Diabetes mellitus (%)	4.2	6.3	9.0	NA†	7.5
LVH (%)	3.5	4.0	7.4	8.3	6.1

Values are unadjusted proportions or means with standard deviations in parentheses. *Only men participated in the study; †NA=not assessed.

whereas in the Novosibirsk study presence of diabetes mellitus was not evaluated for the entire cohort. 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. Height and weight were measured and body mass index (kg/m²) was calculated. In all four centres an electrocardiogram was made. In Cardiff, Kuopio and Novosibirsk, LVH was assessed according to the Minnesota classification system (codes 3.1, 3.3, 3.4).²⁶ In Rotterdam, an automated diagnostic classification system of the Modular Electrocardiogram Analysis System (MEANS) was used in which LVH diagnosis was assessed on the parameters voltage, shape and repolarisation, as detailed elsewhere.^{27, 28} Apart from Rotterdam, a fasting blood sample was taken for determination of serum lipids (total cholesterol, HDL cholesterol). For the present analysis hypertension was defined as a systolic blood pressure of 160 mm Hg or over, or a diastolic blood pressure of 95 mm Hg or over, or current use of blood pressure lowering drugs.

Data analysis

Complete data on both stroke and LVH were available for Cardiff (84 cases/200 controls), Kuopio (60 cases/116 controls), Rotterdam (114 cases/334 controls), and Novosibirsk (62 cases/168 controls).

The analyses were first performed for each centre separately. To identify potential confounding variables, cardiovascular risk factors that were related to stroke were examined using logistic regression models and to LVH using logistic regression models. Factors that were related to both stroke and LVH ($p < 0.10$), and that were not assumed to be in the causal pathway of LVH leading to stroke were considered confounding variables. Systolic blood pressure, diastolic blood pressure, body mass index, current smoking, and diabetes

mellitus were evaluated as potential confounders. LVH as predictor of stroke was studied as a dichotomous variable using logistic regression analysis. Initially adjustments were made for age and sex, and subsequently for potential confounding cardiovascular risk factors.

An interaction term (LVH \times centre) was used to study whether the association between LVH and stroke differed across the four centres (heterogeneity). Interaction term (LVH \times sex) was used to evaluate whether the association differed between men and women. Similar analyses were performed in strata of smoking and hypertension. Results are presented as odds ratios, with their corresponding 95% confidence intervals (95% CI). 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.

In the analysis in which a history of diabetes mellitus was used, analyses were initially performed excluding data from Novosibirsk, because in this centre such data were not available. Additional analyses were performed in which history of diabetes was imputed for the Novosibirsk centre. The imputation was based on the prevalence observed in Cardiff and Kuopio combined, an estimate comparable to what has been reported for Novosibirsk area.¹³ A dummy variable (yes/no) for the imputation was added to the model. As the magnitude of findings did not differ between the two approaches only the latter is presented. The analyses have been performed using STATA version 4.0.

RESULTS

General characteristics of the study populations are given in table 1. Characteristics of the stroke events are presented in table 2. Of all strokes, 73% had been hospitalised. Neuroimaging (CT/MRI) had been performed in 55% of the cases. Among the fatal strokes, 26.2% were a haemorrhagic, 33.8% a cerebral infarctions and 40.0% could not be specified with the available information. The corresponding figures for non-fatal stroke were 9.6%, 80.4% and 10.0%, respectively. In analyses in which

Table 2 Stroke characteristics in each of the participating centres

Characteristic	Cardiff, UK	Kuopio, FIN	Rotterdam, NL	Novosibirsk, RUS	All
Hospitalised (%)	77	90	69	69	75
CT (%)	48	88	72	5	55
First event	74	53	96	61	284
Total stroke	84	60	114	62	320
Fatal	24	11	26	19	80
Non-fatal	60	49	88	43	240
Haemorrhagic	11	13	11	9	44
Ischaemic	57	44	74	45	220
Unspecified	16	3	29	8	56

Values are absolute numbers.

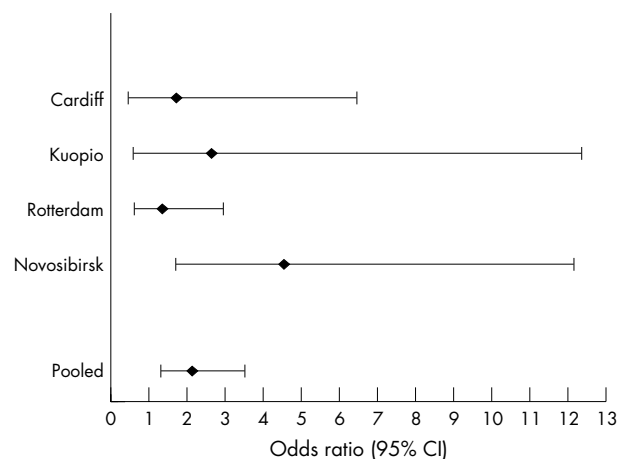


Figure 1 Left ventricular hypertrophy and risk of stroke, by centre. Results are adjusted for age and sex, when appropriate.

information from all centres was combined, age, male sex, systolic blood pressure, diastolic blood pressure, hypertension, current smoking, and history of diabetes mellitus were positively, and significantly ($p < 0.05$) related to stroke. Significant associations with LVH were found for age, systolic blood pressure, diastolic blood pressure and hypertension. Interaction terms indicated no difference in associations between centres ($p = 0.49$) and between men and women ($p = 0.92$).

The association of LVH to stroke for each centre is given in figure 1. In all centres LVH was positively related to the risk of stroke. The centre specific analyses did not always reach the level of statistical significance. The wide confidence interval reflects the limited number of subjects with LVH in each centre. There was no evidence for heterogeneity.

Table 3 describes the association between LVH and risk of stroke for all centres combined. LVH was associated with a twofold increased risk of stroke (odds ratio 2.13 (95% CI 1.29 to 3.50)). Results were similar for first ever stroke. The increased risk seemed to be stronger for fatal stroke than for non-fatal stroke (table 3). When differences in systolic blood pressure and body mass index were taken into account, the

magnitude of the associations between LVH and all types of stroke was attenuated. Additional adjustment for hypertension, smoking and diabetes mellitus did not materially affect the magnitude, direction and significance of the findings (table 3).

Subjects with LVH had a non-significant increased risk of cerebral infarction compared with those without LVH (age and sex adjusted odds ratio 1.68 (95% CI 0.92 to 3.04), $p = 0.09$). The association was more pronounced for fatal than for non-fatal cerebral infarction: odds ratios 3.66 (95% CI 1.19 to 11.2) and 1.44 (95% CI 0.75 to 2.78), respectively. No significant association was found with haemorrhagic stroke (age and sex adjusted odds ratio of 1.52 (95% CI 0.45 to 5.18), $p = 0.50$) or with fatal haemorrhagic stroke (odds ratio 1.03 (95% CI 0.13 to 7.90)) or non-fatal haemorrhagic stroke (odds ratio 2.03 (95% CI 0.45 to 9.06)).

Stratified analyses among smokers and non-smokers showed different tendencies in magnitude in the associations of LVH with stroke (table 4). In smokers, LVH was associated with a 3.47-fold (95% CI 1.49 to 8.09) increased risk of stroke, whereas in non-smokers the risk was 1.61 (95% CI 0.84 to 3.12). The interaction term, however, did not reach statistical significance ($p = 0.15$). No differences in magnitude in association of LVH to stroke was found for men and women nor for hypertension and normotension.

DISCUSSION

This analysis of the EUROSTROKE project indicates that LVH assessed by electrocardiogram is a predictor of stroke. The association seemed to be stronger for fatal stroke than for non-fatal stroke and may be restricted to smokers. Furthermore, no major differences were seen in the magnitude of the association with haemorrhagic stroke and cerebral infarction, if anything the relation with cerebral infarction was more pronounced.

Several aspects of this study should be considered. Firstly, we cannot be sure about the completeness of case ascertainment in each study. The proportion of fatal cases across the centres ranged between 19.3% in Kuopio and 30.6% in Novosibirsk (table 2). Although it is likely that there are true differences in case-fatality of stroke across these countries this may indicate underrepresentation of non-fatal cases. If the selection of non-fatal cases is associated with a lower

Table 3 The association of left ventricular hypertrophy and risk of stroke

	Model I	Model II	Model III	Model IV
All strokes	2.13 (1.29 to 3.50)	1.72 (1.02 to 2.89)	1.62 (0.93 to 2.81)	1.62 (0.43 to 2.81)
First ever	2.13 (1.27 to 3.56)	1.70 (0.99 to 2.92)	1.65 (0.95 to 2.87)	1.57 (0.89 to 2.78)
Fatal	4.02 (2.05 to 7.89)	3.14 (1.55 to 6.36)	2.93 (1.37 to 6.26)	2.76 (1.25 to 6.11)
Non-fatal	1.52 (0.84 to 2.76)	1.19 (0.64 to 2.23)	1.19 (0.64 to 2.24)	1.19 (0.63 to 2.28)
Haemorrhagic	1.52 (0.45 to 5.10)	1.08 (0.30 to 3.86)	1.12 (0.31 to 4.10)	1.10 (0.29 to 4.19)
Cerebral infarction	1.67 (0.92 to 3.04)	1.34 (0.72 to 2.53)	1.34 (0.72 to 2.53)	1.35 (0.72 to 2.59)
Cerebral infarction*	2.21 (1.32 to 3.69)	1.82 (1.07 to 3.11)	1.70 (0.98 to 2.96)	1.74 (0.99 to 3.06)

Odds ratios relative to subjects without LVH, with 95% confidence intervals. *Ischaemic, including subjects with unspecified stroke. Model I: Adjusted for age and sex; Model II: Adjusted for age, sex and systolic blood pressure; Model III: Adjusted for age, sex, systolic blood pressure, and body mass index; Model IV: Adjusted for age, sex, systolic blood pressure, body mass index, diastolic blood pressure, hypertension, current smoking and diabetes mellitus.

Table 4 Stratified analyses of the association of LVH with stroke and cerebral infarction

	Cases/controls	Stroke	Cases/controls	Cerebral infarction
Smoking (yes)	131/245	3.47 (1.49 to 8.08)	91/245	1.91 (0.68 to 5.40)
Smoking (no)	185/567	1.61 (0.84 to 3.11)	126/567	1.71 (0.80 to 3.64)
Hypertension (yes)	181/317	1.89 (1.00 to 3.58)	117/317	1.75 (0.82 to 3.73)
Hypertension (no)	139/501	2.07 (0.91 to 4.71)	103/501	1.46 (0.52 to 4.11)
Men	230/543	2.10 (1.12 to 3.88)	162/543	1.70 (0.82 to 3.50)
Women	90/275	2.23 (0.95 to 5.22)	58/275	1.84 (0.62 to 5.44)

Results are adjusted for ages and for sex, when appropriate.

Table 5 Overview of some population-based studies in which the association between LVH and stroke was studied

First author	Subjects	Age (y)	FUP (y)	Number of strokes	Stroke type	Fatal non-fatal	Prevalence LVH (%)	Main finding on risk	Remarks
Dunn, 1990† ³	1624 M 1650 F	45–74	6.5	29 (any) 17 (any)	NR	Fatal	21.7 12.7	1.8 4.0	Age adjusted Age adjusted
Aronow, 1991† ¹⁰	88 M 238 F	62	3.6	68 (any)	CI	Combined	14.7	2.10 (1.11 to 3.98)*	
Wolf, 1991 ⁸	2372 M 3362 F	55–84	10	213 (first) 259 (first)	NR	Combined	3.5 M 2.9 F	2.32* 2.34*	
Kannel, 1992 ⁷	2372 M 3362 F	35–64	36	NR	NR	Combined	4.8 3.4	5.8* 6.2*	
Truelsen, 1994 ⁹	3015 M 3501 F	55–84	10	286 (first) 188 (first)	NR	Combined	20.6 M 11.3 F	1.32 (1.01 to 1.73)* 1.00 (0.66 to 1.51)*	
Kahn, 1996 ¹¹	459	75–85	10	35	NR	15 Fatal 20 NF	9.2	3.03 (1.09 to 10.6)* 1.1	Unadjusted Unadjusted
Feigin, 1998 ¹³	237 cases 257 controls	68	–	237	CI	Combined	18.1% cases 2.1% controls	1.77 (1.70 to 19.9)*	
Tanne, 1998 ¹⁴	9734 M	≥40	21	282	CI	Fatal	1.87%	2.15 (1.12 to 4.12)*	
Aronow 1999 ¹²	2384	81	44	510	TE	Combined	–	2.8*	

M=men, F=female, FUP=mean duration of follow up in years, NR=not reported, ICH=cerebral haemorrhage, CI=cerebral infarction, TE=thromboembolic. *Adjusted for cardiovascular risk factors (full model); †subjects with hypertension only.

prevalence of the exposure of interest (LVH), it may bias a true positive association towards a reduced odds ratio or a null finding. We have no means to evaluate whether this indeed did take place. Secondly, the association with fatal stroke may be biased towards a positive finding when in the assessment a large proportion of the stroke cases was misclassified—that is, had died from coronary heart disease rather than from stroke. Given the diagnostic procedures in the participating centres this is unlikely to have happened. Thirdly, it has been well established that the sensitivity of the ECG to detect LVH is limited. Data from the Framingham Heart Study indicated a sensitivity of 6.9% and a specificity of 98.8% compared with echocardiography as gold standard.²⁹ The ultimate consequence of this notion is that most probably the reported associations under study are an underestimation of the “true” association; as misclassification occurred in both cases and controls, most probably in a random fashion. Alternatively, a recent paper indicated that ECG-LVH and LVH assessed by echocardiography carry to some extent different prognostic information.³⁰ Finally, we acknowledge that the diagnoses of LVH has been made using different approaches. We used whatever approach had been taken in the individual cohort. Some may have a stronger prognostic implication.³⁰ However, in all cohorts, ECG-LVH was related to risk of stroke without showing differences in associations across the cohorts (fig 1). Strengths of this study are the fairly large number of well diagnosed and classified events for both men and women, presence of data on a large number of potential confounders, a wide age range, and risk factors assessment before the occurrence of the stroke event.

Several studies have evaluated the association between LVH and stroke (table 5). Direct comparison between studies is hampered by differences in population distribution, in selection of population, in methods of assessing LVH, in stroke distribution (fatal/non-fatal, type of stroke) and in adjustment for several potential confounding variables. In general, an increased stroke risk was found among subjects with LVH. In reports of the Framingham Heart study, with different samples from the populations and duration of follow up, LVH was associated with a sixfold increased risk of stroke among middle aged men and women⁷ and with a 2.3-fold increased

risk in the elderly.⁸ Results from Dunn and coworkers in the United Kingdom showed that among hypertensives the relative contribution of LVH to death from stroke decreased with age.³ In the Copenhagen City Heart Study in Denmark weaker than in the Framingham Heart Study, associations were found for men and no relation was seen for women (table 5).⁹ Few studies, however, have distinguished between fatal and non-fatal stroke. In a community-based cohort study among 459 subjects aged 75 to 85 years, who were followed up for 10 years, baseline LVH was associated with a threefold increased risk of fatal stroke ($p=0.07$), whereas a non-significant increased risk of non-fatal stroke was found (odds ratio 1.1).¹¹ The analyses were, however, based on a limited number of fatal ($n=15$) and non-fatal ($n=20$) events. The present EUROSTROKE analysis confirms the increased risk of stroke associated with LVH. In addition, our findings point towards a stronger association of LVH with fatal stroke than with non-fatal stroke, a tendency observed for cerebral infarction only. In this analysis, the increased risk was more pronounced in smokers than in non-smokers. As none of the studies reported such a finding, future studies are needed to confirm this potential effect modification of smoking in stroke risk. It has not been clear by which mechanism smoking increases the risk of stroke. This new finding that LVH may be a condition required for stroke to occur in smokers may suggest that the underlying mechanism is related to either arrhythmias^{31–33} or other cardiac events.

Several hypotheses have been given to explain why LVH predisposes for coronary heart disease and death.⁶ Yet, the mechanisms for stroke may be less clear. Firstly, LVH may be a marker for presence of longstanding increased blood pressure and as such it may reflect cardiovascular end-organ damage, which in itself is associated with increased risk of stroke. Our finding that when differences in blood pressure were taken into account the association between LVH and stroke was reduced, favours this view. Secondly, LVH has been implicated as an important factor in triggering cardiac arrhythmias,^{31–32} which may increase the risk of stroke, in particular ischaemic stroke.

Increased blood pressure has consistently been reported as a major determinant of LVH.⁷ The increased stroke risk of LVH

among smokers further supports the large potential for prevention of stroke by lowering of blood pressure and discouraging starting and encouraging quitting smoking.

In conclusion, this analysis of the EUROSTROKE project indicates that LVH assessed by electrocardiogram is a powerful predictor of stroke. The association seems to be stronger for fatal stroke than for non-fatal stroke and is more pronounced in smokers.

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REFERENCES

- Kannel WB**, Gordon T, Offutt D. Left ventricular hypertrophy by electrocardiogram: prevalence, incidence and mortality in the Framingham Study. *Ann Intern Med* 1969;**71**:89-105.
- Guzik HJ**, Ooi WL, Frishman W, *et al*. Hypertension: cardiovascular implications in a cohort of old old. *J Am Geriatr Soc* 1992;**40**:348-353.
- Dunn FG**, McLenachan J, Isles CG, *et al*. Left ventricular hypertrophy and mortality in hypertension: an analysis of data from the Glasgow Blood Pressure Clinic. *J Hypertens* 1990;**8**:775-82.
- Casale PN**, Devereaux RB, Milner M, *et al*. Value of echocardiographic measurement of left ventricular mass in predicting cardiovascular morbid events in hypertensive men. *Ann Intern Med* 1986;**105**:173-8.
- Pop GA**, Koudstaal PJ, Meeder HJ, *et al*. Predictive value of clinical history and electrocardiogram in patients with transient ischemic attack or minor stroke for subsequent cardiac and cerebral ischemic events. The Dutch TIA trial. *Arch Neurol* 1994;**51**:333-41.
- Levy D**, Salomon M, D'Agostino RB, *et al*. Prognostic implications of baseline electrocardiographic features and their serial changes in subjects with left ventricular hypertrophy. *Circulation* 1994;**90**:1786-93.
- Kannel WB**, Dannenberg AL, Levy D. Population implications of electrocardiographic left ventricular hypertrophy. *Am J Cardiol* 1987;**60**:85-93.
- Wolf PA**, D'Agostino RB, Belanger AJ, *et al*. Probability of stroke: A risk profile from the Framingham Study. *Stroke* 1991;**22**:312-18.
- Truelsen T**, Lindstrom E, Boysen G. Comparison of probability of stroke between Copenhagen City Heart study and the Framingham Study. *Stroke* 1994;**25**:802-7.
- Aronow WS**, Ann C, Kronzon I, *et al*. Congestive heart failure, coronary events and atherosclerotic brain infarction in elderly black and whites with systemic hypertension and with and without echocardiographic and electrocardiographic evidence of left ventricular hypertrophy. *Am J Cardiol* 1991;**67**:295-9.
- Kahn S**, Frishman WH, Weissman S, *et al*. Left ventricular hypertrophy on electrocardiogram: prognostic implication from a 10 year cohort of older subjects: A report of the Bronx Longitudinal Aging Study. *J Am Geriatr Soc* 1996;**44**:524-9.
- Aronow WS**, Ahn C, Kronzon I, *et al*. Association of left ventricular hypertrophy and chronic atrial fibrillation with the incidence of new thromboembolic stroke in 2,384 older persons. *Am J Cardiol* 1999;**84**:468-9.
- Feigin VL**, Wiebers DO, Nikitin P, *et al*. Risk factors for ischemic stroke in a Russian community. *Stroke* 1998;**29**:34-9.
- Tanne D**, Yaari S, Goldbourt U. Risk profile and prediction of long-term ischemic stroke mortality. A 21-year follow-up in the Israeli Ischemic Heart Disease (IHD) project. *Circulation* 1998;**98**:1365-71.
- 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.
- Salonen JT**, Salonen R, Seppänen K, *et al*. High density lipoprotein, HDL₂ and HDL₃ subfractions and the risk of acute myocardial infarction: a prospective population study in Eastern Finnish men. *Circulation* 1992;**84**:129-39.
- 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.
- 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.
- 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.
- Lamberts H**, Wood M, Hofmans-Okkes I. *The international classification of primary care in the European Community*. Oxford: Oxford University Press, 1991.
- WHO MONICA Project Investigators**. World Health Organization MONICA Project (monitoring trends and determinants in cardiovascular disease): a major international collaboration. *J Clin Epidemiol* 1988;**41**:105-14.
- Asplund K**, Tuomilehto J, Steyngmar B, *et al*. Diagnostic criteria and quality control of the registration of stroke events in the MONICA Project. *Acta Med Scand* 1988;**728** (suppl):26-39.
- Feigin VL**, Wiebers DO, Whisnant JP, *et al*. Stroke incidence and 30-day case fatality rates in Novosibirsk, Russia. *Stroke* 1995;**26**:924-9.
- Thorvaldsen P**, Asplund K, Kuulasmaa K, *et al*. Stroke incidence, case fatality, and mortality in the WHO MONICA Project. *Stroke* 1995;**26**:361-7.
- Caerphilly and Speedwell collaborative heart disease studies**. The Caerphilly and Speedwell Collaborative Group. *J Epidemiol Community Health* 1984;**38**:259-62.
- Rose GA**, Blackburn H, Gillum RF, *et al*. Classification of the electrocardiogram for population studies. In: Rose GA, Blackburn H, eds. *Cardiovascular survey methods*. Geneva: World Health Organisation 1968:123-43.
- Van Bommel JH**, Kors JA, van Herpen G. Methodology for the Modular Electrocardiogram Analysis System (MEANS). *Methods Inf Med* 1990;**29**:346-53.
- 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.
- Levy D**, Labib SB, Anderson KM, *et al*. Determinants of sensitivity and specificity of electrocardiographic criteria for left ventricular hypertrophy. *Circulation* 1990;**81**:1144-6.
- Sundström J**, Lind L, Årnlöv J, *et al*. *Circulation* 2001;**103**:2346-51.
- Levy D**, Anderson KM, Savage SA, *et al*. Risk of ventricular arrhythmias in left ventricular hypertrophy: the Framingham Heart Study. *Am J Cardiol* 1987;**60**:560-65.
- Siegel D**, Cheitlin MD, Black DM, *et al*. Risk of ventricular arrhythmias in hypertensive men with left ventricular hypertrophy. *Am J Cardiol* 1990;**65**:742-7.
- Oliver MF**. Prevention of coronary heart disease: Propaganda, promises, problems and prospects. *Circulation* 1986;**73**:1-9.