EVIDENCE BASED PUBLIC HEALTH POLICY AND PRACTICE

Age and follow-up time affect the prognostic value of the ECG and conventional cardiovascular risk factors for stroke in adult men

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Objectives: To explore whether the predictive power of mid-life ECG abnormalities and conventional cardiovascular risk factors for future stroke change over a 30-year follow-up period, and whether a repeated examination improves their predictive power.
Design and setting: Longitudinal population-based study.
Participants: 2322 men aged 50 years, with a follow-up period of 30 years. 1221 subjects were re-examined at age 70 years
Main outcome measure: Risk for fatal and non-fatal stroke during three decades of follow-up. Investigations included resting ECG and traditional cardiovascular risk factors.
Results: When measured at age 50 years, ST segment depression and T wave abnormalities, together with ECG-left ventricular hypertrophy, were of importance only during the first 20 years, but regained importance when re-measured at age 70 years. Blood pressure was a significant predictor for stroke over all three decades of follow-up. In elderly people only, there is evidence that apolipoprotein A1 may protect from future stroke.
Conclusion: Mid-life values for blood pressure and ECG abnormalities retain their predictive value over long follow-up periods even though they improved in predictive power when re-measured in elderly people. Despite lower prevalence, ECG abnormalities had greater impact at age 50 years than at age 70 years. By contrast, apolipoprotein A1 was protective for future stroke only at age 70 years.

Even though there is a trend towards decreasing mortality due to stroke in many countries, the number of patients with stroke is growing because of changes in the age structure of Western populations.[1] The clinical syndrome of stroke consists of different pathologies, the two main types being ischaemic stroke, which accounts for 72–82%,[2] and haemorrhagic stroke. Most ischaemic strokes are caused by thromboemboli arising from atheromatous disease. Non-atheromatous causes of stroke include cardiac arrhythmias, cardiomyopathies or intracranial vessel disease. Clinical evidence of atherosclerosis in one vascular bed is probably a reflection of more widespread atheromatous disease.[3] However, risk factor patterns for complications of atherosclerosis may differ in the various parts of the cardiovascular tree.[4] Also, risk factors for cardiovascular disease (CVD) may differ between young and older subjects, and stroke, congestive heart failure, atrial fibrillation and chronic nephropathy may become more important in very old subjects.[5]

ECG abnormalities have been shown to be associated with increased long-term risk of mortality due to coronary heart disease (CHD) and CVD,[6–8] and the prognostic value of major ECG findings for CVD and CHD have been shown to be more powerful than well-established risk factors.[9 10] Even though ECG findings are not a direct cause of stroke, the presence of CHD could be a good predictor of stroke since the two diseases could have common causes.

The effect of follow-up time and re-measurement of the ECG and conventional risk factors on their predictive value for stroke is especially important to understand, since many subjects with traditional cardiovascular risk factors will have died of cardiac disease before reaching the age at which stroke commonly occurs.

Our hypothesis was that the impact of risk factors for stroke might change over time, more so for some variables than for others. Hence, we studied how the impact of risk factors for stroke changed over time, with special emphasis on ECG abnormalities, using data from the Uppsala Longitudinal Study of Adult Men (ULSAM), a cohort with 30 years of follow-up. The subjects in ULSAM were examined at age 50 years and re-examined 20 years later, allowing us to investigate how risk factors measured in mid-life changed in predictive power during three decades of follow-up, and to study the impact of cardiovascular risk factors in the same cohort with baseline at two different time points, at ages 50 and 70 years

METHOD

Study sample and design

All 50-year-old men, born between 1920 and 1924, in Uppsala, Sweden, were invited to participate in ULSAM, aimed at identifying risk factors for CVD.[11] Of the invited subjects, 2322 (82%) participated in 1970–3. Twenty years later, between 1991 and 1995, eligible participants were invited for re-examination at age 70 years. Of these, 1221 (73%) participated. Between the two surveys, 422 had died and 219 had moved. Official registry data were available, the censored date being 31 December 2001.

Information on the men born between 1920 and 1924, who had been hospitalised for cerebrovascular disease during the 10 years before the investigation, was collected from hospital

Abbreviations: ApoA1, apolipoprotein A1; apoB apolipoprotein B, CHD, coronary heart disease; CVD, cardiovascular disease; ECG-LVH, ECG-left ventricular hypertrophy; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure; TIA, transient ischaemic attack; ULSAM, Uppsala Longitudinal Study of Adult Men

records, and two participants who had had a cerebrovascular disease were excluded. Drugs were classified according to the current list of pharmaceutical specialities available in Sweden. Only daily long-term medication was included.

Baseline investigations and laboratory methods

Investigations at age 50 years

These investigations have been described extensively elsewhere.[11] Twelve-lead resting ECGs were recorded and coded according to the Minnesota code.[12 13] Abnormal Q/QS pattern was defined as a Q/QS wave with a certain magnitude according to the Minnesota codes 1.1–1.3, ST segment depression as 4.1–4.2, T wave abnormalities as 5.1–5.3 and atrial fibrillation as 8.3. High R-amplitude codes 3.1/3.3, together with 4.1–4.2, were considered to indicate ECG-left ventricular hypertrophy (ECG-LVH). Concentrations of serum low-density lipoprotein (LDL)-cholesterol, high-density lipoprotein (HDL)-cholesterol and apolipoproteins A1 (apoA1) and B (apoB) were measured on a subset of serum samples that had been stored since sampling, initially in liquid nitrogen and later in freezers.

The overall incidence rate for stroke in subjects where serum samples were analysed for LDL-cholesterol, HDL-cholesterol and apoA1 and apoB compared with subjects where it was not, was 0.6 and 0.65 per 100 patient-years, respectively. Diabetes mellitus was defined as fasting blood glucose $\geq$6.1 mmol/l[14] and/or pharmacological treatment for diabetes mellitus.

Smoking habits were collected through interviews. In middle-aged men 51% were smokers. The percentage of ex-smokers (those who had stopped smoking at least one month ago) was 23.2%, and 25.8% had never smoked.

Investigations at age 70 years

The cohort was re-investigated at age 70 years, at which time all investigations performed at age 50 years, including standard resting ECG, were repeated. At age 70 years, the apoB/apoA1 ratio was only determined in a random sample of 551 subjects. Technical problems with one of the freezers led to a random loss of samples, accounting for the reduced amount of samples available for apolipoprotein analyses. At the age of 70 years glucose levels were analysed as fasting plasma glucose levels, so the criteria for diabetes mellitus were changed to take this into account. Diabetes mellitus was defined according to latest guidelines as fasting plasma glucose $\geq$7 mmol/l[14] and/or pharmacological treatment for diabetes mellitus.

End point and follow-up

All men who were free from stroke at baseline were followed for the first occurrence of fatal or non-fatal any-cause stroke, using the Swedish cause-of-death registry and the hospital discharge registry data. Stroke was defined as *International classification of disease*, ninth revision codes 431 and 433–436 or 10th revision I61, I63–I66, thereby including both ischaemic (81%) and haemorrhagic stroke (19%). Transitory cerebral ischaemic attacks (58 cases) were included among ischaemic stroke. Separate analyses were also carried out for ischaemic stroke. The maximal follow-up period was 31.7 years. The study was divided into two parts (fig 1). In part I of the study, the follow-up period was divided into three consecutive periods, between ages 50 and 60, 60 and 70 and 70 and 80. Part II of the study was divided into two follow-up periods. Part IIa, with a maximum follow-up time of 23.8 years, covered the period from date of the first examination at age 50 years (n = 2322) to date of the first non-fatal or fatal stroke event or second examination at age 70 years; and part IIb, with a maximum follow-up time of 10.4 years, covered the period from baseline at age 70 years (n = 1221) until event date or censored date.

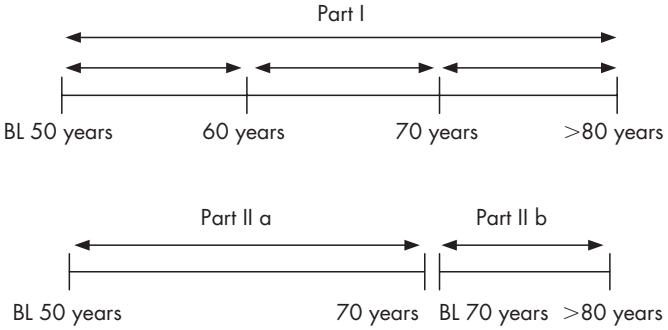

Figure 1 Study design. BL, baseline, outcome: fatal and non-fatal any-cause stroke/ischaemic stroke.

Only men who were free from stroke at baseline at age 70 years were included in part IIb.

Statistical analyses

The statistical analyses were carried out using Stata V.8.0. Continuous variables were standardised to 1 SD, with the mean value being zero (mean = 0) and 1 SD being 1 (1SD = 1). Univariate Cox's proportional hazards regression analyses were used to determine the relationship of various risk factors and subsequent any-cause stroke and ischaemic stroke in the different follow-up periods. The proportional hazard assumption was checked for each of the variables for the whole follow-up period (0–30 years) and for each of the follow-up periods using the test for Schoenfeld's residuals. Also, to test for proportionality within each of the follow-up periods, time-dependent covariates were generated by creating interactions of the predictors and a function of survival time, and time-dependant covariates were included in all multivariate models and tested for significance using a likelihood-ratio test. Testing the time-independent covariates is equivalent to testing for zero slope in a generalised linear regression of the scaled Schoenfeld's residuals on functions of time. All factors with $p < 0.15$, in the different follow-up periods in parts I and II, were evaluated for independence in a backward stepwise multiple model. In multivariate analyses, hazard ratios (HRs) were adjusted for age at entry and only variables with $p < 0.05$ were allowed to stay in the models. To investigate whether the relationship between the independent risk factors and stroke outcomes was maintained if subjects with a history of myocardial infarction were excluded, multivariate analyses were repeated after excluding subjects with first myocardial infarction before the 50-year examination or before first stroke events.

To further analyse the relative difference in impact of the specific ischaemic ECG abnormalities on stroke prognosis in young and elderly people, attributable fractions were estimated by dividing the incidence difference of stroke in subjects with and without the specific ECG abnormality by the incidence of stroke (I_S) in subjects with the specific ECG abnormality:

$$\text{Attributable fraction} = \frac{(I_S \text{ in subjects with ECG abnormality}) - (I_S \text{ in subjects without ECG abnormality})}{(I_S \text{ in subjects with ECG abnormality})}$$

RESULTS

During the total follow-up period of up to 30 years, 1019 (43.9%) had died and 343 had either been hospitalised or died from any-cause stroke, and of these, 221 were due to ischaemic stroke. Of the stroke events, 13% were fatal (n = 45). Baseline

Table 1 Baseline characteristics of cardiovascular risk factors at 50- and 70-year-surveys

Characteristics	Survey at age 50 (all subjects at age 50 included)	n	Survey at age 50 (only subjects attending both surveys included)	n	Survey at age 70	n	p Value for t test (age 50 vs age 70 years)†
ECG items							
Q/QS wave pattern (%)	1.3	2322	0.9	1221	12.8	1139	
ECG-LVH (%)	1.2		0.5		6.5		
ST segment depression (%)	2.3		1.2		14.3		
T wave abnormal (%)	5.9		3.8		16.0		
AF (%)	0.3		0.3		4.6		
Conventional cardiovascular risk factors	Mean (SD)		Mean (SD)		Mean (SD)		
BMI (kg/m^2)	25.0 (3.2)	2322	24.9 (2.9)	1221	26.3 (3.4)	1215	<0.001
SBP supine (mm Hg)	133.1 (18.1)	2321	131.5 (16.7)	1221	146.8 (18.5)	1216	<0.001
DBP supine (mm Hg)	83.7 (11.2)	2321	82.7 (10.5)	1221	83.8 (9.5)	1216	0.007
Fasting glucose (mmol/l)*	5.5 (1.0)	2314	5.0 (0.7)	1217	5.8 (1.5)	1219	<0.001
Fasting insulin (μU/ml)	13.1 (7.8)	1794	12.5 (7.0)	985	13.0 (8.3)	1206	0.01
Serum triglycerides (mmol/l)	1.9 (1.2)	2322	1.8 (0.9)	1221	1.4 (0.8)	1220	<0.001
Serum total cholesterol (mmol/l)	6.9 (1.3)	2322	6.8 (1.3)	1221	5.8 (1.0)	1220	<0.001
HDL cholesterol (mmol/l)	1.4 (0.4)	1880	1.4 (0.4)	988	1.3 (0.3)	1218	<0.001
LDL cholesterol (mmol/l)	5.3 (1.3)	1880	5.2 (1.2)	988	3.9 (0.9)	1214	<0.001
ApoA1 (g/l)	1.4 (0.3)	1826	1.4 (0.2)	965	1.3 (0.2)	548	<0.001
ApoB (g/l)	1.2 (0.3)	1826	1.2 (0.3)	965	1.03 (0.2)	551	<0.001
ApoB/apoA1 ratio	0.89 (0.26)	1826	0.88 (0.24)	965	0.82 (0.2)	548	<0.001
Prevalence of smoking (%)	51.1	2322	44.6	1221	20.8	1181	
Diabetes mellitus (%)	5.4	2315	4.2	1217	9.8	1219	

AF, atrial fibrillation; ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; BMI, body mass index; DBP, diastolic blood pressure; ECG, electrocardiogram; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LVH, left ventricular hypertrophy; SBP, systolic blood pressure.
*Data given are plasma concentrations (blood-glucose concentrations at age 50 were multiplied by a conversion-factor of 1.11 to be comparable with plasma, according to IFCC recommendation, *Clinical Chemistry* 2005 **51**:1573–6).
†p Value for one-sample, two-sided, t test for H_0 = mean at survey age 50–mean at survey at age 70 years = 0

characteristics at ages 50 and 70 years are displayed in table 1. There was a significant difference for all the continuous cardiovascular risk factors between ages 50 and 70 years

According to the test of Schoenfeld's residuals, proportional hazards assumption was fulfilled for each variable and follow-up period. Also, the insertion of time-dependent variables into the multivariate models for the different follow-up periods did not affect the models significantly.

Part I: predictive value of mid-life risk factors over three different follow-up periods

The incidence rates for any-cause stroke increased for the three different decades of follow-up: 0.17, 0.62 and 1.3/100 person-years at risk. Tables 2 and 3 show the results from the univariate analyses, for any-cause stroke (including transient ischaemic attack (TIA) and haemorrhagic), and for ischaemic stroke. Analyses carried out with the outcome of ischaemic stroke showed a trend similar to any-cause stroke.

When any-cause stroke was considered, the ECG abnormalities (except atrial fibrillation), smoking and diabetes mellitus were significant predictors during the first two decades of follow-up, whereas blood pressure was a significant predictor for all three decades in the univariate analyses (table 2). A similar pattern was seen when ischaemic stroke was analysed as the end point (table 3).

In stepwise multivariate analyses with any-cause stroke included, systolic blood pressure (SBP) was an independent predictor during all follow-up periods, even though the impact of SBP measured in middle age decreased with time. The presence of ST segment depression, T wave abnormality and smoking were significant independent predictors during the first two decades, whereas the only variable that still had a predictive value for events occurring between the ages of 70 and 80 years was SBP (table 4). In a similar multiple regression model including only ischaemic stroke cases, a similar picture was seen, but in that case, atrial fibrillation and diabetes mellitus were significant predictors during the first decade of follow-up (table 5).

Parts IIa and IIb: comparison between risk factors in midlife and at age 70 years

For part IIa, with a follow-up period from baseline at age 50 to 70 years, the incidence rate of any-cause stroke was 0.38/100 person-years, whereas for part IIb with a follow-up period from baseline at age 70 years to the censor date, it was threefold higher: 1.22/per 100 person-years.

Tables 6 and 7 show the results from the univariate analyses for any-cause stroke and for ischaemic stroke.

In the univariate analyses for any-cause stroke, ECG-LVH, ST segment depression and T wave abnormalities were significant predictors for stroke when evaluated both at age 50 and at age 70 years (tables 6 and 7). On the contrary, atrial fibrillation was a significant predictor at age 70 years only. According to the attributable fraction, the impact of ECG abnormalities for future stroke was higher at age 50 than 70 years.

Blood pressure was a significant predictor for any-cause stroke both at age 50 and at 70 years, whereas fasting glucose and insulin, smoking and diabetes mellitus were predictors at age 50 years only. On the other hand, apoA1 was a protective factor at age 70 years only. A similar trend was seen when only cases with ischaemic stroke were analysed (table 7), but for ischaemic stroke, fasting insulin and glucose as well as diabetes mellitus were significant predictors at both ages 50 and 70 years

In stepwise multiple regression analyses with any-cause stroke, ST depression, T wave abnormalities, SBP and smoking were independent predictors of stroke when measured at age 50 years, while atrial fibrillation and LDL-cholesterol were independent predictors at age 70 years. ApoA1 protected against stroke in elderly people. Similar data were obtained when only cases with ischaemic stroke were analysed, with the exception that diabetes mellitus was an independent predictor

Table 2 Baseline cardiovascular risk factors associated with future fatal and non-fatal any-cause stroke (including transient ischaemic attack and haemorrhagic stroke) over a total period of 30 years of follow-up and divided into three different follow-up periods

Follow-up period	0–30 (age period 50–80 years)		0–9.9 (age period 50–60 years)		10–19.9 (age period 60–70 years)		20–30 (age period 70–80 years)	
No. of cases	343		40		122		181	
PYAR	57 003		23 317		19 719		13 966	
Characteristics	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI†)	P Value	HR (95% CI)	p Value
ECG items								
Q/QS on ECG	2.71 (1.21 to 6.08)	0.016	4.66 (1.12 to 19.3)	0.03	3.07 (0.98 to 9.67)	0.06	1.33 (0.19 to 9.50)	0.8
ECG-LVH	5.68 (3.11 to 10.4)	<0.001	16.0 (6.25 to 40.8)	<0.001	5.39 (1.99 to 14.6)	0.001	2.27 (0.56 to 9.14)	0.3
ST depression	4.60 (2.89 to 7.31)	<0.001	11.3 (4.92 to 25.2)	<0.001	5.10 (2.49 to 10.5)	<0.001	2.04 (0.8 to 5.51)	0.2
T wave abnormality	2.58 (1.82 to 3.66)	<0.001	4.33 (2.00 to 9.40)	<0.001	3.56 (2.16 to 5.87)	<0.001	1.36 (0.70 to 2.66)	0.4
Atrial fibrillation	1.68 (0.24 to 11.98)	0.6						
Conventional cardiovascular risk factors								
BMI	1.16 (1.05 to 1.30)	0.004	1.23 (0.92 to 1.64)	0.2	1.18 (0.99 to 1.41)	0.06	1.14 (0.98 to 1.32)	0.1
SBP supine	1.39 (1.27 to 1.52)	<0.001	1.67 (1.34 to 2.07)	<0.001	1.51 (1.31 to 1.73)	<0.001	1.21 (1.05 to 1.40)	0.008
DBP supine	1.34 (1.21 to 1.48)	<0.001	1.53 (1.17 to 1.99	0.002	1.41 (1.20 to 1.65)	<0.001	1.24 (1.07 to 1.43)	0.004
Fasting glucose	1.11 (1.01 to 1.22)	0.04	1.21 (1.02 to 1.44)	0.03	1.13 (0.99,1.30)	0.07	1.02 (1.86 to 1.22)	0.8
Fasting insulin	1.16 (1.04 to 1.29)	0.007	1.31 (1.05 to 1.62)	0.014	1.17 (0.98 to 1.38)	0.08	1.10 (0.93 to 1.30)	0.3
Triglycerides	1.06 (0.94 to 1.19)	0.3	1.11 (0.93 to 1.33	0.2	1.00 (0.81 to 1.24)	0.98	1.07 (0.88 to 1.29)	0.5
Cholesterol	1.03 (0.93 to 1.15)	0.5	0.91 (0.66 to 1.25)	0.5	1.08 (0.90 to 1.28)	0.4	1.04 (0.89 to 1.20)	0.6
HDL	0.99 (0.88 to 1.13	0.96	0.88 (0.60 to 1.27)	0.5	1.01 (0.82 to 1.23)	0.95	1.02 (0.86 to 1.21)	0.9
LDL	1.03 (0.92 to 1.17)	0.6	0.90 (0.63 to 1.28)	0.6	1.09 (0.90 to 1.32)	0.4	1.03 (0.87 to 1.22)	0.7
ApoA1	0.97 (0.86 to 1.10)	0.8	0.79 (0.55 to 1.14)	0.2	1.02 (0.83 to 1.24)	0.9	0.79 (0.84 to 1.18)	0.9
ApoB	1.03 (0.91 to 1.16)	0.6	1.04 (0.74 to 1.45)	0.8	1.00 (0.82 to 1.22)	0.97	1.04 (0.88 to 1.23)	0.6
ApoB/ApoA1	1.05 (0.93 to 1.18)	0.4	1.15 (0.84 to 1.59)	0.4	1.05 (0.86,1.28)	0.6	1.02 (0.86 to 1.22)	0.8
Smoking	1.35 (1.10 to 1.68)	0.005	2.96 (1.46 to 6.06)	0.003	1.45 (1.01 to 2.08)	0.04	1.11 (0.83 to 1.49)	0.5
DM	1.69 (1.13 to 2.51)	0.01	2.57 (1.00 to 6.56)	0.05	1.93 (1.04 to 3.58)	0.04	1.29 (0.68 to 2.45)	0.4

ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; BMI, body mass index; DBP, diastolic blood pressure; DM, diabetes mellitus; ECG, electrocardiogram; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LVH, left ventricular hypertrophy; PYAR, patient years at risk; SBP, systolic blood pressure.
HRs with 95% CI derived from univariate Cox's proportional hazards regression were applied to variables standardised to 1 SD. Due to the low number of ECGs with atrial fibrillation at age 50 (n = 7), it was only possible to determine HRs for atrial fibrillation for the total follow-up period and for the first 10 years of follow-up

Table 3 Baseline cardiovascular risk factors associated with future fatal and non-fatal ischaemic stroke (excluding transient ischaemic attack and haemorrhagic stroke) over a total period of 30 years of follow-up and divided into three different follow-up periods

Follow-up period	0–30 (age period 50–80 years)		0–9.9 (age period 50–60 years)		10–19.9 (age period 60–70 years)		20–30 (age period 70– 80 years)	
No. of cases	221		16		75		130	
PYAR	54 873		22 174		18 933		13 766	
Characteristics	HR (95% CI)	P Value	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value
ECG items								
Q/QS on ECG	3.67 (1.51 to 8.93)	0.004	5.85 (0.77 to 44.3)	0.09	4.83 (1.52 to 15. 4)	0.008	1.92 (0.27 to 13.8)	0.5
ECG-LVH	7.64 (3.92 to 14.90)	<0.001	39.3 (12.7 to 122)	<0.001	6.74 (2.12 to 12.4)	0.001	3.18 (0.79 to 12.9)	0.1
ST depression	6.29 (3.78 to 10.47)	<0.001	32.5 (11.8 to 89.5)	<0.001	6.26 (2.72 to 14.4)	<0.001	2.82 (1.04 to 7.62)	0.04
T wave abnormality	3.02 (1.99 to 4.58)	<0.001	10.7 (3.89 to 29.5)	<0.001	4.38 (2.41 to 7.97)	<0.001	1.28 (0.57 to 2.91)	0.6
Atrial fibrillation	2.71 (0.38 to 19.31)	0.3	25.7 (3.39 to 194)	0.002				
Conventional cardiovascular risk factors								
BMI	1.26 (1.11 to 1.43)	<0.001	1.28 (0.81 to 2.00)	0.3	1.33 (1.08 to 1.64)	0.008	1.21 (1.02 to 1.44)	0.03
SBP supine	1.47 (1.31 to 1.64)	<0.001	2.04 (1.52 to 2.74)	<0.001	1.62 (1.36 to 1.91)	<0.001	1.26 (1.07 to 1.48)	0.005
DBP supine	1.43 (1.27 to 1.62)	<0.001	2.06 (1.41 to 2.74)	<0.001	1.51 (1.23 to 1.84)	<0.001	1.29 (1.09 to 1.53)	0.003
Fasting glucose	1.18 (1.07 to 1.32)	0.002	1.39 (1.16 to 1.66)	<0.001	1.14(0.95 to 1.36)	0.2	1.15 (0.97 to 1.36)	0.1
Fasting insulin	1.22 (1.09 to 1.37)	0.001	1.46 (1.16 to 1.83)	0.001	1.20 (0.99 to 1.45)	0.06	1.17 (0.98 to 1.40)	0.08
Triglycerides	1.09 (0.95 to 1.24)	0.2	1.12 (0.86 to 1.46)	0.4	1.05 (0.83 to 1.33)	0.7	1.10 (0.89 to 1.37)	0.4
Cholesterol	1.01 (0.89 to 1.16)	0.9	0.69 (0.40 to 1.18)	0.2	1.08 (0.86 to 1.35)	0.5	1.02 (0.86 to 1.22)	0.8
HDL	0.95 (0.81 to 1.11)	0.5	0.80 (0.45 to 1.44)	0.5	0.92 (0.69 to 1.22)	0.6	0.99 (0.80 to 1.21)	0.9
LDL	0.99 (0.85 to 1.15)	0.9	0.66 (0.37 to 1.16)	0.2	1.11 (0.86 to 1.42)	0.4	0.98 (0.81 to 1.20)	0.9
ApoA1	0.97 (0.83 to 1.13)	0.7	0.71 (0.39 to 1.31)	0.3	0.97 (0.74 to 1.26)	0.8	0.99 (0.81 to 1.22)	0.96
ApoB	1.01 (0.87 to 1.18)	0.9	0.88 (0.50 to 1.54)	0.7	0.99 (0.77 to 1.29)	0.96	1.03 (0.85 to 1.26)	0.7
ApoB/ApoA1	1.04 (0.89 to 1.21)	0.6	1.13 (0.67 to 1.90)	0.6	1.07 (0.83 to 1.38)	0.6	1.01 (0.83 to 1.24)	0.9
Smoking	1.24 (0.95 to 1.61)	0.1	4.37 (1.25 to 15.3)	0.02	1.17 (0.75 to 1.84)	0.5	1.12 (0.79 to 1.58)	0.5
DM	2.39 (1.55 to 3.69)	<0.001	5.85 (1.89 to 18.1)	0.002	2.56 (1.28 to 5.14)	0.008	1.86 (0.97 to 3.55)	0.06

ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; BMI, body mass index; DBP, diastolic blood pressure; DM, diabetes mellitus; ECG, electrocardiogram; HDL, high density lipoprotein; LDL, low-density lipoprotein; LVH, left ventricular hypertrophy; PYAR, patient years at risk; SBP, systolic blood pressure.
HRs with 95% CI derived from univariate Cox's proportional hazards regression were applied to variables standardised to 1 SD. Owing to the low number of ECGs with atrial fibrillation at age 50 years (n=7), it was only possible to determine HRs for atrial fibrillation for the total follow-up period and for the first 10 years of follow-up.

at age 50 years (table 8). Also, similar trends, with similar point estimates and overlapping confidence intervals, were obtained if subjects with a history of myocardial infarction before the first stroke event were excluded from the multivariate analyses. A total of 16% of subjects with any-cause stroke and 19% with ischaemic stroke had a non-fatal myocardial infarction before the first stroke event (data not shown).

DISCUSSION

This study shows that the effect of traditional risk factors in middle-aged men change over prolonged follow-up periods and when re-measured at old age. Furthermore, the study also points out that ECG changes, such as ST segment depression and T wave abnormalities, are also important risk factors for stroke.

Consistent with another population-based study carried out in Swedish men aged 47–55 years in 1970–3,[15] high blood pressure, smoking and diabetes mellitus were associated with future stroke in middle-aged men, whereas high cholesterol levels were not. In our cohort, atrial fibrillation, a well-known risk factor for stroke,[15 16] was found to be of importance only in elderly people, probably owing to low prevalence in mid-life subjects (n = 7). SBP was an important risk factor for any-cause stroke and for ischaemic stroke over three decades of follow-up when measured at age 50 years. Although being of major importance during the first decades of follow-up when evaluated at age 50 years, ST segment depression, T wave abnormalities and ECG-LVH regained significance when re-measured at age 70 years. Despite lower prevalence, ECG abnormalities had greater impact on risk at age 50 years than

Table 4 Independent predictors for fatal and non-fatal any-cause stroke (including transient ischaemic attack and haemorrhagic stroke) over a period of 30 years of follow-up divided into different follow-up periods

Follow-up period	0–30 (age period 50–80 years)		0–9.9 (age period 50–60 years)		10–19.9 (age period 60–70 years)		20–30 (age period 70–80 years)	
Characteristics	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value
SBP supine	1.38 (1.26 to 1.51)	<0.001	1.50 (1.19 to 1.89)	0.001	1.47 (1.27 to 1.70)	<0.001	1.21 (1.05 to 1.40)	0.008
ST segment depression	3.36 (2.08 to 5.42)	<0.001	5.88 (2.30 to 15.0)	<0.001				
T wave abnormality					2.62 (1.55 to 4.42)	<0.001		
Smoking	1.51 (1.21 to 1.87)	<0.001	3.22 (1.57 to 6.62)	0.001	1.61 (1.12 to 2.30)	0.01		

SBP, systolic blood pressure.
HRs with 95% CIs from Cox's proportional hazards regression were applied to variables standardised to 1 SD. Stepwise multiple regression analysis were performed for each decade of follow-up and only variables retained in the models are presented (p<0.05).

Table 5 Independent predictors for fatal and non-fatal ischaemic stroke (excluding transient ischaemic attack and haemorrhagic stroke) over a period of 30 years of follow-up divided into different follow-up periods

Follow-up period	0–30 (age period 50–80 years)		0–9.9 (age period 50–60 years)		10–19.9 (age period 60–70 years)		20–30 (age period 70–80 years)	
Characteristics	**HR (95% CI)**	**p Value**	**HR (95% CI)**	**p Value**	**HR (95% CI)**	**p Value**	**HR (95% CI)**	**P Value**
SBP supine	1.37 (1.22 to 1.55)	<0.001	1.59 (1.13 to 2.24)	0.008	1.53 (1.28 to 1.83)	<0.001	1.26 (1.07 to 1.48)	0.006
BMI	1.15 (1.00 to 1.31)	0.04						
ST segment depression	4.35 (2.57 to 7.39)	<0.001	12.82 (3.73 to 43.5)	<0.001				
T wave abnormality					3.18 (1.71 to 5.92)	<0.001		
Atrial fibrillation			15.07 (1.77 to 128)	0.01				
Diabetes mellitus	1.72 (1.02 to 2.48)	0.042	3.30 (1.01 to 10.8)	0.05				
Smoking	1.44 (1.10 to 1.88)	0.008	5.68 (1.56 to 20.7)	0.008				

BMI, body mass index; SBP, systolic blood pressure.
HRs with 95% CIs from Cox's proportional hazards regression were applied to variables standardised to 1 SD. Stepwise multiple regression analysis were performed for each decade of follow-up and only variables retained in the models are presented ($p<0.05$).

at age 70 years. In elderly people only, LDL-cholesterol was an independent risk factor for future stroke, whereas apoA1 seemed to protect against future stroke.

The strength of our study is that the subjects have been followed for >30 years with repeated investigations. An obvious limitation of our study is the lack of women. There was no validation of the individual stroke cases. However, in previous studies, stroke, defined by combining data from the Cause of Death Registry and Hospital Discharge Registry in Sweden, has been shown to be an efficient, validated alternative to revised hospital discharge notes and death certificates.[17] The association between risk factors and any-cause stroke will be substantially influenced by ischaemic stroke, the dominant stroke subtype in our study population, so it was not surprising that the same results were obtained whether any-cause stroke cases were analysed or when only those with ischaemic stroke were used in the models. The only main difference was a more pronounced impact of glucose and insulin when only ischaemic stroke cases were considered.

Differences in risk factor patterns for stroke between studies may depend on discrepancies in classification of stroke, dominant stroke subtype in the study population and different follow-up time or differences in baseline age.[18] Since stroke usually occurs later in life than CHD some of the participants in the cohort studies will have died from CHD before reaching the age when stroke occurs, thereby reducing the impact of some traditional cardiovascular risk factors on future development of stroke. This could explain why risk factors such as smoking, diabetes mellitus and high body mass index (BMI) were significant predictors in mid-life but not at the age of 70 years.

Table 6 Hazard ratio for baseline characteristics at ages 50 and 70 years for fatal and non-fatal any-cause stroke (including transient ischaemic attack and haemorrhagic stroke) over different follow-up periods.

Follow-up period	Part IIa (n = 2320)			Part IIb (n = 1148)		
No. of cases	**172**			**106**		
PYAR	**44 206**			**8667**		
Characteristics	**HR (95% CI)**	**P Value**	**AF (%)**	**HR (95% CI)**	**p Value**	**AF (%)**
ECG items						
Q/QS on ECG	3.51 (1.44 to 8.55)	0.006	66	1.50 (0.88 to 2.57)	0.1	33
ECG-LVH	8.41 (4.29 to 16.5)	<0.001	86	2.75 (1.53 to 4.94)	0.001	52
ST depression	6.61 (3.88 to 11.2)	<0.001	82	2.12 (1.32 to 3.42)	0.002	46
T wave abnormal	3.66 (2.41 to 5.55)	<0.001	70	2.17 (1.38 to 3.43)	0.001	47
Atrial fibrillation	2.93 (0.41 to 20.9)	0.3	59	4.48 (2.49 to 8.06)	<0.001	59
Conventional cardiovascular risk factors						
BMI	1.24 (1.08 to 1.43)	0.003		1.09 (0.90 to 1.32)	0.4	
SBP supine	1.55 (1.38 to 1.74)	<0.001		1.47 (1.23 to 1.77)	<0.001	
DBP supine	1.43 (1.26 to 1.64)	<0.001		1.27 (1.05 to 1.55)	0.01	
Fasting glucose	1.16 (1.04 to 1.29)	0.009		1.13 (0.96 to 1.32)	0.2	
Fasting insulin	1.20 (1.05 to 1.38)	0.006		1.10 (0.98 to 1.23)	0.1	
Triglycerides	1.06 (0.92 to 1.22)	0.4		0.89 (0.72 to 1.10)	0.3	
Cholesterol	1.03 (0.88 to 1.20)	0.7		1.07 (0.88 to 1.30)	0.5	
HDL cholesterol	0.97 (0.81 to 1.15)	0.7		0.87 (0.71 to 1.06)	0.2	
LDL cholesterol	1.02 (0.86 to 1.20)	0.8		1.18 (0.98 to 1.43)	0.08	
ApoA1	0.92 (0.78 to 1.10)	0.4		0.69 (0.52 to 0.91)	0.009	
ApoB	0.99 (0.84 to 1.17)	0.9		1.11 (0.86 to 1.44)	0.4	
ApoB/ApoA1	1.08 (0.92 to 1.27)	0.4		1.32 (1.02 to 1.70)	0.03	
Smoking	1.59 (1.17 to 2.15)	0.003		1.27 (0.81 to 2.00)	0.3	
Diabetes mellitus	1.99 (1.19 to 3.34)	0.009		1.55 (0.88 to 2.72)	0.13	

AF, attributable fraction (calculated only for ECG abnormalities); ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; BMI, body mass index; DBP, diastolic blood pressure; ECG, electrocardiogram; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LVH, left ventricular hypertrophy; PYAR, patient years at risk; SBP, systolic blood pressure.
HRs with 95% CIs from Cox's proportional hazards regression were applied to variables standardised to 1 SD.
Subjects with a pacemaker at age 70 years were excluded from further analyses in part IIb.

Table 7 Hazard ratio for baseline characteristics at age 50 and age 70 years for fatal and non-fatal ischaemic stroke (excluding transient ischaemic attack and haemorrhagic stroke) over different follow-up periods

Follow-up period	Part IIa (n = 2320)			Part IIb (n = 1148)		
No. of cases	**98**			**81**		
PYAR	**42 24 321**			**8573**		
Characteristics	**HR (95% CI)**	**p Value**	**AF (%)**	**HR (95% CI)**	**p Value**	**AF (%)**
ECG items						
Q/QS on ECG	4.94 (1.81 to 13.5)	0.002	75	1.45 (0.78 to 2.69)	0.2	27
ECG-LVH	12.5 (5.8 to 27.0)	<0.001	90	3.37 (1.82 to 6.27)	<0.001	53
ST depression	9.97 (5.44 to 18.3)	<0.001	88	2.31 (1.36 to 3.93)	0.002	46
T wave abnormal	5.14 (3.11 to 8.50)	<0.001	78	2.15 (1.28 to 3.62)	0.004	44
Atrial fibrillation	5.10 (0.71 to 36.6)	0.1	76	5.07 (2.67 to 9.63)	<0.001	59
Conventional cardiovascular risk factors						
BMI	1.36 (1.14 to 1.64)	0.001		1.04 (0.98 to 1.11)	0.2	
SBP supine	1.69 (1.47 to 1.95)	<0.001		1.02 (1.01 to 1.03)	0.001	
DBP supine	1.57 (1.32 to 1.87)	<0.001		1.02 (0.99 to 1.05)	0.06	
Fasting glucose	1.21 (1.06 to 1.38)	0.004		1.13 (1.01 to 1.27)	0.03	
Fasting insulin	1.27 (1.09 to 1.47)	0.002		1.02 (1.00 to 1.03)	0.03	
Triglycerides	1.09 (0.92 to 1.29)	0.3		0.87 (0.63 to 1.19)	0.4	
Cholesterol	0.99 (0.81 to 1.22)	0.9		1.14 (0.91 to 1.42)	0.3	
HDL cholesterol	0.88 (0.69 to 1.13)	0.99		0.70 (0.36 to 1.36)	0.3	
LDL cholesterol	0.97 (0.77 to 1.22)	0.2		1.29 (1.00 to 1.64)	0.04	
ApoA1	0.87 (0.69 to 1.11)	0.3		0.21 (0.05 to 0.85)	0.03	
ApoB	0.95 (0.76 to 1.20)	0.7		1.67 (0.43 to 6.53)	0.5	
ApoB/ApoA1	1.09 (0.87 to 1.36)	0.4		3.62 (0.93 to 14.1)	0.06	
Smoking	1.33 (0.89 to 1.98)	0.2		1.36 (0.82 to 2.27)	0.2	
Diabetes mellitus	2.91 (1.62 to 5.22)	<0.001		2.75 (1.32 to 5.74)	0.007	

AF, Attributable fraction (calculated only for ECG abnormalities); ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; BMI, body mass index; DBP, diastolic blood pressure; ECG, electrocardiogram; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LVH, left ventricular hypertrophy; PYAR, patient years at risk; SBP, systolic blood pressure.
HRs with 95% CIs from Cox's proportional hazards regression were applied to variables standardised to 1 SD.
Subjects with pacemaker at age 70 years were excluded from further analyses in part IIb.

Consistent with other studies,[19–22] we found smoking to be associated with stroke, but only in middle-aged men. This finding could be explained not only by premature death but also by a decrease in smoking with age. The data should not be interpreted that smoking is not a risk factor in old age. Diabetes mellitus was associated with stroke in middle-aged men only; however, considering the similar point estimates and overlapping confidence intervals it is not possible to exclude the significance in elderly people. Similarly, as found in another study,[23] BMI in middle-aged men was associated with stroke.

The roles of serum cholesterol and lipoprotein fractions as risk factors for stroke are far less consistent and more controversial[18 19 24–26] than those for myocardial infarction. The Prospective Studies Collaboration, involving >45 prospective observational cohorts and 450 000 individuals, was not able to demonstrate an association between stroke and cholesterol levels even though they recognise that the lack of an overall relationship might conceal a positive association with ischaemic stroke together with a negative association with haemorrhagic stroke.[25] Also, analysis of the EUROSTROKE Project could not disclose an association of total cholesterol with fatal, non-fatal, haemorrhagic or ischaemic stroke[26] even though, in men, an increase in HDL-cholesterol was associated with a non-significant reduced risk of stroke in all centres. In our study, none of the lipid variables were associated with stroke in midlife. However, LDL-cholesterol was an independent predictor in multivariate analysis in elderly people. Also, in our study, the apoB/apoA1 ratio, with apoA1 driving the significance of the ratio, was found to be a significant predictor for stroke in elderly people. Recent studies have shown that the apoB/apoA1 ratio, which indicates the balance between atherogenic apoB-containing particles and atheroprotective apoA1-containing particles, may be a better predictor for CVD than the more traditional markers for dyslipidaemia.[27–30] Qureshi *et al*[31] were unable to demonstrate any statistically significant association between either apoA1 or apoB and stroke.[31] However, their baseline investigations were performed at a younger age. A case–control study carried out in a Chinese population found that apoA1 decreased the risk of stroke. In that study, 57% of the patients were older than 70 years,[32] further supporting our finding of an important protective role of apoA1 in elderly people. Our study also supports the recent findings by Walldius *et al*,[28] where the apoB/apoA1 ratio was shown to be associated with stroke.

ST segment depression and T wave abnormalities were seen both in LVH and myocardial ischaemia.[33] In a study with up to 14 years of follow-up, in apparently healthy individuals with essential hypertension, LVH diagnosed by ECG or echocardiography was shown to confer an excess risk for stroke and TIA, independently of other individual risk factors.[34] The association been ECG-LVH and stroke in the EUROSTROKE project has been found to be more pronounced in smokers.[35] However, it needs to be emphasised that the causal inter-relationship between ECG-LVH and specific stroke types is complex and different mechanisms may be involved.

The EUROSTROKE Project, even though the results indicated that ECG-LVH was a predictor for stroke,[35] did not consider ECG characteristics necessary in screening for stroke in the general population, since ECG abnormalities did not contribute to the prediction of stroke according to their model of risk scores.[36] Our findings suggest that a standard resting ECG could play an important role in identifying patients at increased risk for stroke and that even minor ECG abnormalities may be of importance when assessing the individual patient's global burden of risk. ECG abnormalities together with low apoA1 levels could help identify elderly patients at increased risk for stroke and thereby contribute to reduction of suffering and disability if effective preventive measures are instituted.

Table 8 Independent predictors for fatal and non-fatal any-cause stroke and ischaemic stroke, in multivariate analyses, at ages 50 and 70 years over different follow-up periods

	Any-cause stroke Part IIa Age 50–70		Any-cause stroke Part IIb Age 70 years to censored data		Ischaemic stroke Part IIa Age 50–age 70 years		Ischaemic stroke Part IIb Age 70 years to censored data	
Characteristics	**HR (95% CI)**	**p Value**	**HR (95% CI)**	**p Value**	**HR (95% CI)**	**p Value**	**HR (95% CI)**	**p Value**
ST depression	2.45 (1.20 to 5.00)	0.014			2.91 (1.27 to 6.67)	0.01		
T wave abnormality	1.82 (1.04 to 3.19)	0.035			2.27 (1.16 to 4.46)	0.02		
SBP	1.48 (1.31 to 1.67)	<0.001			1.53 (1.31 to 1.79)	<0.001		
Smoking	1.77 (1.30 to 2.40)	<0.001			1.59 (1.06 to 2.39)	0.03		
Diabetes mellitus					1.92 (1.04 to 3.56)	0.04		
Atrial fibrillation			8.95 (4.39 to 18.26)	<0.001			10.11 (4.53 to 22.6)	<0.001
LDL			1.39 (1.05 to 1.84)	0.02			1.47 (1.07 to 2.02)	0.02
ApoA1			0.59 (0.43 to 0.82)	0.002			0.58 (0.40 to 0.84)	0.004

ApoA1, apolipoprotein A1; LDL, low-density lipoprotein; SBP, systolic blood pressure.
HRs with 95% CIs from Cox's proportional hazards regression were applied to variables standardised to 1 SD and adjusted for age at entry.

What this paper adds

- During a follow-up period of over 30 years, systolic blood pressure retained its predictive value for stroke.
- ECG ischaemic abnormalities were of importance only during the first 20 years, but regained importance when re-measured at age 70 years.
- In the elderly people only, apolipoprotein A1 protected against future stroke.

Policy implications

- Our findings suggest that a standard resting ECG could play an important role in assessing the patients' global burden of risk for stroke.
- ECG abnormalities, together with low apolipoprotein A1 levels, could help to identify elderly patients at increased risk for stroke.

In conclusion, mid-life values for blood pressure and ECG abnormalities retain their predictive value over long follow-up periods, even though they improved in predictive power when re-measured in elderly people. Despite lower prevalence, ECG abnormalities had greater impact at age 50 years than at age 70 years. By contrast, there was evidence that ApoA1 may protect from future stroke in elderly people.

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Contributions: All authors participated in the design of the study and helped to draft the manuscript. All authors read and approved the final manuscript. CSM performed the statistical analyses and JH provided statistical expertise.

Ethical approval: All subjects have given informed consent and the ethics committee of the Faculty of Medicine, Uppsala University, has approved the Uppsala Longitudinal Study of Adult Men.

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APHORISM OF THE MONTH

The age of Hygieia

It is now time that we replace public health's aggressive disease-orientated Aesculapius' symbol of medicine with the peaceful countenance of Hygieia, who more accurately reflects the commitment of public health.

Lowell Levin