# Risk factors for stroke in middle aged British men

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## Abstract

***Objective*—To determine the risk factors for stroke in a cohort representative of middle aged British men.**

***Design*—Prospective study of a cohort of men followed up for eight years.**

***Setting*—General practices in 24 towns in England, Wales, and Scotland (the British regional heart study).**

***Subjects*—7735 men aged 40-59 at screening, selected at random from one general practice in each town.**

***Main outcome measure*—Fatal and non-fatal strokes.**

***Results*—110 of the men had at least one stroke; there were four times as many non-fatal as fatal strokes. The relative risk of stroke was 12·1 in men who had high blood pressure (systolic blood pressure ≥160 mm Hg) and were current smokers compared with normotensive, non-smoking men. Diastolic blood pressure yielded no additional information, and former cigarette smokers had the same risk as men who had never smoked. Heavy alcohol intake was associated with a relative risk of stroke of 3·8 in men without previously diagnosed cardiovascular disease. Men with pre-existing ischaemic heart disease had an increased risk of stroke, but only when left ventricular hypertrophy on electrocardiography was also present.**

***Conclusions*—Systolic blood pressure, cigarette smoking, and left ventricular hypertrophy on electrocardiography in men with pre-existing ischaemic heart disease were found to be the major risk factors for stroke in middle aged British men. Heavy alcohol intake seemed to increase the risk of stroke in men without previously diagnosed cardiovascular disease. A large proportion of strokes should be preventable by controlling blood pressure and stopping smoking.**



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## Introduction

According to a consensus statement on stroke, "Every five minutes someone in the United Kingdom has a stroke. It is the cause of one in eight deaths and constitutes a formidable burden of disability and misery for patients, their carers, and the wider community."[1] The overall mortality from stroke in the United Kingdom fell by about 20% between 1976 and 1986 but is still double that in the United States.[2] Compared with the number of studies on ischaemic heart disease there have been few major prospective studies investigating the precursors of stroke. Although half of all first strokes occur in people aged 76 years and over, most of the established factors predisposing to stroke are present much earlier in life. Action towards preventing stroke should therefore begin as early as possible. We have attempted to identify factors predisposing to stroke in a population of middle aged men drawn from general practices in Great Britain. Although the incidence of stroke is relatively low in this age group, it represents the time of life at which intervention may be feasible, acceptable, and beneficial.

## Subjects and methods

During 1978-80, 7735 men aged 40-59 years were selected at random from one general practice in each of 24 towns in England, Wales, and Scotland for a prospective study of cardiovascular disease (the British regional heart study). The criteria for selecting the towns, general practices, and subjects, as well as the methods of data collection, have previously been reported.[3] Only those men who were unable to participate because of severe physical or mental handicap were excluded from the study. No attempt was made to exclude those with cardiovascular or other disease or those receiving regular treatment. Research nurses administered to each man a standard questionnaire, which included questions on medical history, smoking habits, and alcohol intake. Several physical measurements were made and blood taken for determination of biochemical and haematological variables. After the initial examination all men, whether or not they had evidence of cardiovascular disease or other disorders at the first examination, were followed up for eight years to determine mortality from all causes and cardiovascular morbidity.[4]

Information on death was collected through the established tagging procedures provided by the NHS registers in Southport (for England and Wales) and Edinburgh (for Scotland). Deaths from stroke comprised all those coded as ICD 430-8 (ninth revision of the International Classification of Diseases). Non-fatal episodes comprised all those cerebrovascular events which produced a neurological deficit that was present for more than 24 hours. Fatal episodes were those in which death occurred within 28 days after the onset of symptoms. No attempt was made to separate strokes into specific categories—that is, subarachnoid haemorrhage, cerebral haemorrhage, or cerebral thrombosis or infarction—as the information required to do so is not available in population studies of this kind. Body mass index calculated as weight/(height)$^2$ (kg/m$^2$) was used as an index of relative weight.

*Cigarette smoking*—Men were classified into those who had never smoked, former cigarette smokers, and current cigarette smokers by using <20, 20, and >20 cigarettes per day as cut off points.

*Alcohol*—On the basis of a questionnaire on drinking patterns men were classified according to their alcohol intake: never or occasional (<1 drink/week), light (1-20 drinks/week), moderate (21-42 drinks/week), or heavy (>42 drinks/week).[5] A drink was half a pint of beer, a glass of wine, or a single tot of spirits.

*Social class*—The longest held occupation of each man was recorded at screening and the men were grouped into one of six social classes: I, II, or III non-manual (together designated "non-manual") or III

manual, IV, or V (together designated "manual"). Men whose longest held occupation had been in the armed forces were excluded from the social class analysis.

*Blood pressure*—Blood pressure was recorded by using a London School of Hygiene sphygmomanometer with the subject seated and the arm supported and cushioned on a table. Two successive readings were taken and the mean used in the analysis with adjustment for interobserver variation.[6] Diastolic blood pressure was recorded at the disappearance of sounds (phase V).

*Pre-existing cardiovascular disease*—The men were asked whether a doctor had ever told them that they had had a stroke, ischaemic heart disease (angina, heart attack, myocardial infarction, coronary thrombosis), hypertension, or other heart disease. They also completed a standardised World Health Organisation (Rose) chest pain questionnaire to determine whether they had angina or had had a possible myocardial infarction, and each had a three orthogonal lead electrocardiogram recorded, which was analysed by computer in the university department of medical cardiology at Glasgow Royal Infirmary. The electrocardiographic diagnosis of left ventricular hypertrophy was based on a scoring system in which abnormalities such as high amplitude QRS complexes, ST-T changes, and abnormal QRS axis were included.[7] Men were classified according to the presence of pre-existing ischaemic heart disease into three groups: (1) those with no pre-existing ischaemic heart disease; (2) those with angina diagnosed by a doctor or apparent in chest pain questionnaires,[8] or evidence of possible or definite myocardial ischaemia or possible myocardial infarction in the electrocardiogram; and (3) those with recall of a doctor's diagnosis of myocardial infarction or evidence of definite infarction in the electrocardiogram (those with definite evidence of previous myocardial infarction).

*Antihypertensive drugs*—In all, 375 of the men were taking antihypertensive drugs regularly.

*Statistical methods*—Adjustment was carried out by using multiple logistic regression models. Hypothesis testing and estimation of 95% confidence intervals were carried out by using the standard error estimate for the logistic coefficient estimates.

## Results

Of 7735 men, 110 had at least one stroke during the eight years of observation, and there was a steep age gradient in the incidence (table I). There were 52 men with a history of stroke before initial screening—that is, with recall of a previous diagnosis of stroke—of whom three had further strokes during follow up. In the remaining 107 men who had a stroke during follow up the first stroke was fatal in 23—that is, they died within 28 days after onset, giving a ratio of about four non-fatal strokes to one fatal stroke. The steep age gradient was seen for both fatal and non-fatal strokes.

TABLE I—*Incidence of stroke in men during eight years after entry into study, according to age at initial screening*

| Age | No of men | No who had a stroke | Incidence/ 1000/year |
|---|---|---|---|
| 40-44 | 1838 | 6 | 0·4 |
| 45-49 | 1898 | 15 | 1·0 |
| 50-54 | 1974 | 34 | 2·2 |
| 55-59 | 2024 | 55 | 3·4 |

### BLOOD PRESSURE

Figure 1 shows the incidence of stroke (per 1000 per year), adjusted for age, by grouped systolic blood pressure, with the majority of strokes (60%) occurring in men with systolic blood pressure ≥160 mm Hg. Below this value there was no evidence of an increasing trend. After adjustment for the effect of increasing systolic blood pressure with age men with systolic blood pressure between 160 mm Hg and 180 mm Hg had about four times the risk of stroke of men with blood pressure below 160 mm Hg. Those with values above 180 mm Hg had a sixfold greater risk of stroke than men with values below 160 mm Hg.

A similar but weaker relation was seen with diastolic blood pressure. A multiple logistic model incorporating systolic and diastolic blood pressures and age resulted in a logistic coefficient for systolic blood pressure which was significantly positive ($p<0·0001$), whereas the coefficient for diastolic blood pressure was negative and not significant ($p=0·28$). The relation between blood pressure and stroke seems to be predicted by systolic blood pressure, and knowledge of the diastolic blood pressure does not increase ability to predict the risk of stroke.

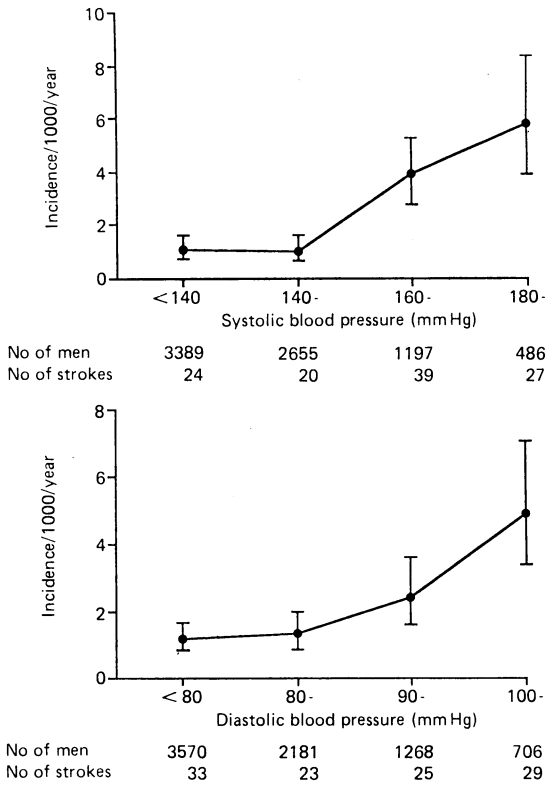


FIG 1—*Age adjusted incidence of stroke during eight years of follow up, according to (top) systolic and (bottom) diastolic blood pressure. Bars are 95% confidence intervals*

### CIGARETTE SMOKING

Current cigarette smokers had more than a twofold risk of stroke compared with men who have never smoked (table II), but the increasing trend with the amount smoked was not significant ($p=0·2$). Former cigarette smokers had a similar risk to those who had never smoked cigarettes. Adjustment for blood pressure has a negligible effect on the associations between cigarette smoking and stroke, as there is little relation between blood pressure and cigarette smoking. Table III shows that the risk related to smoking was

TABLE II—*Age adjusted incidence of stroke in men during eight years after entry into study, according to smoking habits*

| Cigarette smoking status | No of men | No who had a stroke | Incidence/ 100 year | 95% Confidence interval |
|---|---|---|---|---|
| Never smoked | 1819 | 12 | 1·0 | (0·6 to 1·7) |
| Former smoker | 2715 | 26 | 1·1 | (0·7 to 1·6) |
| Smoker of <20/day | 1188 | 24 | 2·4 | (1·6 to 3·6) |
| Smoker of 20/day | 835 | 18 | 2·6 | (1·7 to 4·2) |
| Smoker of >20/day | 1162 | 30 | 3·5 | (2·4 to 4·9) |

TABLE III—*Relative risk of stroke in men according to systolic blood pressure and smoking status. Figures in parentheses are number of strokes/number of men*

| Systolic blood pressure (mm Hg) | Current cigarette smoker | |
|---|---|---|
| | No | Yes |
| <160 | 1·0 (17/3614) | 2·4 (31/2558) |
| ≥160 | 3·6 (21/917) | 12·1 (41/622) |

present in men with and without raised systolic blood pressure (≥160 mm Hg). The combination of cigarette smoking and a raised systolic blood pressure resulted in a more than 10-fold increase in the risk of stroke compared with that in normotensive men who were not cigarette smokers.

### ALCOHOL INTAKE

The age adjusted incidence of stroke showed no consistent trend with alcohol intake (table IV), although the highest incidence was seen in the heavy drinkers and this was significantly higher than the incidence in non-drinkers and occasional drinkers (p=0·03). Adjustment for age and cigarette smoking had some effect on the rates, leaving the heavy drinkers with a 53% higher risk of stroke than the non-drinkers and occasional drinkers, which was not significant (p=0·1). After additional adjustment for systolic blood pressure this small excess in rate of stroke was halved.

TABLE IV—*Incidence of stroke in men during eight years after entry into study, according to alcohol consumption, social class, and presence of pre-existing heart disease*

| | | | Incidence/1000/year | |
|---|---|---|---|---|
| | No of men | No who had a stroke | Adjusted for age | Adjusted for age, systolic blood pressure, and smoking |
| Alcohol consumption: | | | | |
| None/occasional | 2311 | 34 | 1·8 | 1·9 |
| Light | 2544 | 28 | 1·3 | 1·9 |
| Moderate | 2042 | 28 | 1·8 | 1·7 |
| Heavy | 832 | 20 | 3·3 | 2·4 |
| Social class: | | | | |
| Non-manual | 3061 | 30 | 1·2 | 1·5 |
| Manual | 4428 | 77 | 2·2 | 2·0 |
| Pre-existing ischaemic heart disease: | | | | |
| None | 5708 | 59 | 1·4 | 1·5 |
| Angina/myocardial ischaemia | 1482 | 33 | 2·6 | 2·3 |
| Definite myocardial infarction | 410 | 18 | 4·2 | 4·1 |

Men with cardiovascular disease are known to reduce their alcohol intake either completely or to occasional drinking, and therefore we analysed alcohol intake in relation to stroke for men with and without recall of a doctor's previous diagnosis of ischaemic heart disease, stroke, or hypertension (fig 2). Those with a previous diagnosis had a risk of stroke more than three times greater than that of the other men, and there was a significant difference in the association between alcohol consumption and stroke in men with a diagnosis compared with men without one (test for interaction p=0·01). In the men with a previous diagnosis there was a significantly higher risk of stroke in the non-drinkers and occasional drinkers compared with the light drinkers, which is in keeping with our previous finding that men with cardiovascular disease tend to become non-drinkers or occasional drinkers.[5] In the men with no previous diagnosis of cardiovascular disease there was a nearly fourfold increased risk in the heavy drinkers compared with the non-drinkers and occasional drinkers (relative risk 3·8). This excess fell to twofold after adjustment for age, cigarette smoking, and systolic blood pressure but remained significant (p=0·03).

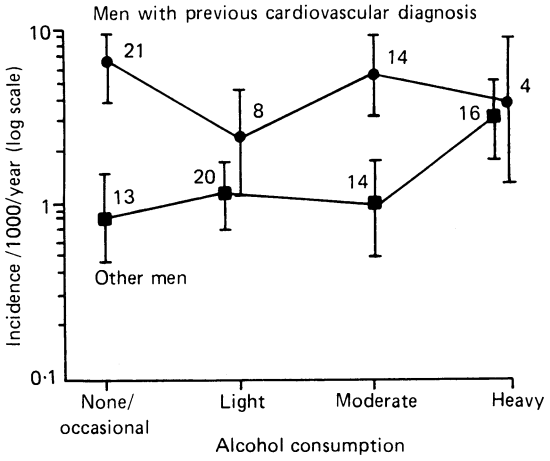


FIG 2—*Age adjusted incidence of stroke with (n=1307) and without (n=6422) previous diagnosis of ischaemic heart disease, stroke, or hypertension during eight years after entry into study, according to alcohol consumption. Bars are 95% confidence intervals. Figures are numbers of men with stroke events*

### SOCIAL CLASS

Men in the manual social classes had almost twice the risk of stroke of men in the non-manual classes (table IV) (p=0·01). Adjustment for differences in cigarette smoking, age, and blood pressure seemed to account for about half of this excess, and the difference after adjustment was no longer significant (p=0·17).

### PRE-EXISTING ISCHAEMIC HEART DISEASE

Men with definite evidence of a previous myocardial infarction had a fourfold increase in risk of stroke compared with men with no pre-existing ischaemic heart disease (table IV). Men with pre-existing angina or with electrocardiographic evidence of myocardial ischaemia had a twofold increase in risk. Overall, men with any evidence of pre-existing ischaemic heart disease had a more than twofold increase in risk. While these differences could in small part be attributed to the association of age, systolic blood pressure, and cigarette smoking with pre-existing ischaemic heart disease, there remained a significant excess risk of stroke after these other risk factors had been taken into account.

### LEFT VENTRICULAR HYPERTROPHY

At screening 463 men had left ventricular hypertrophy with or without secondary ST-T changes on electrocardiography. Of these, 18 had a stroke. Even after adjustment for age and systolic blood pressure this represented a significantly higher incidence of stroke than that in the 7223 men without left ventricular hypertrophy, who experienced 92 strokes (2·9 *v* 1·7/1000/year; p=0·05). The effect of left ventricular hypertrophy was considered separately in those with and without pre-existing ischaemic heart disease (table V). The association between left ventricular hypertrophy and stroke was present only in those with pre-existing ischaemic heart disease (interaction test, p=0·003).

TABLE V—*Incidence of stroke (1000/year) adjusted for age and systolic blood pressure in men with or without left ventricular hypertrophy on electrocardiography, according to whether they had pre-existing heart disease. Figures in parentheses are number of strokes/number of men*

| Pre-existing ischaemic heart disease | Left ventricular hypertrophy | |
|---|---|---|
| | Not present | Present |
| Not present | 1·5 (54/5414) | 1·1 (4/313) |
| Present | 2·2 (38/1809) | 7·9 (14/150) |

### PARENTAL DEATH

The risk of stroke in men whose father or mother had died of heart problems, stroke, or other or unknown causes was compared with that in men whose fathers or mothers, or both, were still alive at the time of screening. There was no evidence that a parent's cause of death had any effect on a man's risk of stroke, either with or without adjustment for the man's systolic blood pressure and smoking status.

### OTHER FACTORS

Comparison of the age adjusted mean values of

serum total cholesterol, high density lipoprotein cholesterol, and triglyceride concentrations; body mass index; and packed cell volume in those who had had a stroke with those in other subjects showed no evidence of a relation with the risk of stroke. The mean serum glucose concentration (non-fasting) was significantly higher in men who had had a stroke than in other men (6·05 *v* 5·62 mmol; p=0·01), but this was not significant after adjustment for age and systolic blood pressure. However, this is consistent with the study's finding that men in whom diabetes mellitus had been diagnosed had a higher incidence of stroke (3/118).

PREVIOUS STROKE

At the initial examination 52 men reported that they had already suffered a stroke. Twenty one men had hypertension (systolic blood pressure ≥160 mm Hg) at screening, of whom 11 were receiving regular antihypertensive treatment. Half of the men who had had a previous stroke (27) were current smokers and two thirds (32) had pre-existing ischaemic heart disease. Of the nine men with a previous stroke who were under 50 years of age, eight were smokers at the time of screening. During the eight years of follow up 11 of the 52 men died: seven of ischaemic heart disease and one of a further stroke.

THE MULTIFACTORIAL RISK OF STROKE

Our findings confirm the importance of systolic blood pressure, cigarette smoking, and left ventricular hypertrophy with the presence of pre-existing ischaemic heart disease in the risk of stroke. Interestingly only 12 of the 110 men who suffered a stroke were current nonsmokers with a systolic blood pressure <160 mm Hg on screening. Of these 12, only six were free of pre-existing ischaemic heart disease and diabetes on screening.

## Discussion

Raised systolic blood pressure and current cigarette smoking were clearly the critical risk factors for stroke in these middle aged British men. Raised systolic blood pressure can readily be detected, and its reduction reduces the incidence of stroke.[10] Former cigarette smokers in this study and in other studies have the same risk of stroke as men who have never smoked, and thus giving up smoking is of great importance in reducing the risk of stroke. Clearly the problem is preventable, and when we consider that for every person who dies of stroke there are almost four who survive, often with a considerable burden of disability, the need to prevent stroke seems incontrovertible. The burden of disability from stroke is far greater than is indicated by mortality data. Furthermore, declining mortality from stroke may not necessarily reflect the same rate of decline in the incidence of stroke.

BLOOD PRESSURE

The importance of raised blood pressure in the aetiology of stroke is well established,[11] and a large number of studies have emphasised the superiority of systolic blood pressure as an indicator of risk over diastolic blood pressure.[12-14] A review and reversal of the current practice of using measurements of diastolic blood pressure alone as an indicator for therapeutic intervention is long overdue. Studies in middle aged Dutch men and women have shown that isolated raised systolic blood pressure, even in the presence of normal diastolic blood pressure, is a significant predictor of mortality.[15] The British regional heart study data do not suggest any increasing trend in incidence of stroke in those with systolic blood pressure <160 mm Hg or diastolic blood pressure <90 mm Hg. A recent review of seven major prospective observational studies, together containing 843 stroke events, showed that there was a continuous positive relation between diastolic blood pressure and stroke down to levels as low as 76 mm Hg in six of the studies.[11] No data were provided for systolic blood pressure.

CIGARETTE SMOKING

There are several reports incriminating cigarette smoking in the aetiology of stroke, and our findings are in keeping with the evidence of a strong association, with a suggestion (not significant) of an increasing trend in risk with the amount smoked. Former smokers in our study had a similar risk to that of those who had never smoked cigarettes, but in a recent Australian case-control study of 422 cases of first episode atherothrombotic brain infarction the trend towards reduction in risk of stroke on giving up smoking was not significant and appreciable risk was still apparent 10 years after giving up smoking.[16] A recent overview (meta-analysis) of 32 separate studies showed considerable differences between the types of stroke and the risk associated with cigarette smoking.[17] The greatest relative risk (2·9) was of subarachnoid haemorrhage, followed by cerebral infarction (1·9). In the Medical Research Council mild hypertension trial cigarette smoking was significantly associated with stroke in both men and women, but no specific analysis was presented for former smokers.[18]

ALCOHOL

The heavy drinkers (>42 drinks/week) in this study had a higher incidence of stroke than those in the other categories of drinking, and this finding is in keeping with the observations in Birmingham, United Kingdom,[19] Japan,[20] and Honolulu.[21,22] About half of the excess risk in heavy drinkers in the present study can be explained, in statistical terms, by the increased systolic blood pressure. The fact that there remains in men without previously diagnosed cardiovascular diseases or hypertension a significant effect of heavy alcohol consumption after adjustment for age, cigarette smoking, and systolic blood pressure could indicate a risk with heavy alcohol consumption over and above its hypertensive effect. It could, however, also reflect imprecise characterisation of a subject's systolic blood pressure because it was measured on only one occasion.[23]

SOCIAL CLASS

There is little information about social class effects on cerebrovascular disease in Britain. Manual workers in the present study had an increased risk of stroke compared with non-manual workers, and adjustment for well recognised differences in cigarette smoking and blood pressure seem to account for about half of this excess.

PRE-EXISTING CARDIOVASCULAR DISEASE

Almost all studies of stroke have shown that previous stroke or ischaemic heart disease constitutes an important risk factor, independently of current smoking or blood pressure. Men who had had ischaemic heart disease, stroke, or hypertension diagnosed by a doctor were at considerably increased risk of stroke (fig 2), but more detailed analysis indicates that ischaemic heart disease was a risk factor for stroke only when it was associated with left ventricular hypertrophy on electrocardiography. This strongly suggests that longstanding hypertension is the prime factor in the risk of stroke rather than the presence of ischaemic heart disease itself.

Left ventricular hypertrophy found on electrocardiography was shown in the Framingham study to have an association with the risk of transient ischaemic attack and stroke in both men and women over 30 years

of follow up.[24,25] There has been no suggestion, however, that the effect exists only in those with pre-existing ischaemic heart disease, as our results indicate, although this specific possibility may not have been studied.

### OTHER RISK FACTORS

The relation between serum total cholesterol concentration and stroke has long been uncertain, and earlier American data have shown no significant association with all types of stroke or with cerebral infarction.[26] In the men screened for the multiple risk factor intervention trial deaths caused by stroke showed a U shaped relation with the serum total cholesterol concentration, with the highest mortality in those with concentrations <4·2 mmol/l and ≥7·74 mmol/l.[27] The risk of death from thrombotic stroke increased significantly with increasing concentration. For cerebral haemorrhage the death rate was highest in those in the lowest blood cholesterol concentration category (<4·14 mmol/l), and thereafter there was no discernible trend with increasing concentration. The present study showed no relation between stroke and serum total cholesterol or serum triglyceride concentrations, and the Melbourne (case-control) and Whitehall (prospective) studies also did not show such a relation.[16,28] The Whitehall study showed that a blood glucose concentration >5·4 mmol/l two hours after a 50 g oral glucose load was independently associated with risk of stroke.[28] In the present study patients who had a stroke had higher non-fasting glucose concentrations than the other men, but this finding was not significant after adjustment for age and systolic blood pressure.

### IMPLICATIONS FOR PREVENTION

An extensive review pooling the data from nine randomised trials of antihypertensive treatment suggested that the effects of long term raised blood pressure on the cerebral vasculature are mostly reversible over five to six years of blood pressure reduction.[11] The Medical Research Council mild hypertension trial also reported that treatment of mild hypertension (diastolic blood pressure 90-109 mm Hg) is effective in lowering the incidence of stroke.[18] This trial also showed that in some 20% of those with mild hypertension in the placebo group blood pressure rose during the period of the study to the level at which treatment was indicated by the protocol. There seems good reason for those with hypertension to have lower blood pressure, particularly if this can be achieved effectively without recourse to drugs. Thus there can be little argument about the need for weight reduction in hypertensive patients who are overweight[29] and for alcohol reduction in those with moderate or heavy intakes.[30]

That cigarette smoking is of considerable importance in stroke now seems undeniable, and the conclusion that "the best advice which can be given to patients with mild hypertension is that they should not smoke" seems to be wholly justified.[31] The combination of hypertension and cigarette smoking is even more hazardous in those with left ventricular hypertrophy on electrocardiography and pre-existing ischaemic heart disease, to whom advice regarding cigarette smoking must be particularly pertinent. In our study and in others the relation between cigarette smoking and stroke seems to diminish fairly rapidly after stopping smoking, although the Melbourne case-control study suggests that the process is more gradual.[16] Interestingly, half of the men entering this study with a previously diagnosed stroke were still smoking cigarettes, and cigarette smoking seemed to be of considerable importance in men under 50 years of age who had a stroke and in those who died. Stroke should rank far more prominently among the consequences of cigarette smoking. Above all, stroke is a multifactorial disease in which systolic blood pressure and cigarette smoking play the critical parts, and the evidence strongly suggests that a large proportion of strokes are preventable.

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