Smoking, atherosclerosis and risk of abdominal aortic aneurysm

A. J. Lee*, F. G. R. Fowkes*, M. N. Carson*, G. C. Leng* and P. L. Allan†

*Wolfson Unit for Prevention of Peripheral Vascular Diseases, Department of Public Health Sciences, Medical School, Edinburgh, U.K.; †Department of Radiology, The Royal Infirmary of Edinburgh NHS Trust, Lauriston Place, Edinburgh, U.K.

Aims The role of cardiovascular risk factors and atherosclerosis in the aetiology of abdominal aortic aneurysms is not well understood. The aim of this study was to determine the association between atherosclerosis and aortic aneurysm in the general population and the extent to which cardiovascular risk factors might increase the risk of aneurysm independently of an effect on atherosclerotic disease.

Methods and Results In the Edinburgh Artery Study, 1592 men and women aged 55–74 years were followed prospectively over a period of 5 years. Forty subjects were identified as having an abdominal aortic aneurysm and, for each, five controls were randomly selected. Cases showed a higher prevalence of cardiovascular disease ($P \leq 0.001$) and had a lower ankle brachial pressure index ($P \leq 0.01$). Current and recent ex-cigarette smokers had an increased risk of aortic aneurysm compared with long time ex-smokers and never smokers (odds ratio 3·08, 95% CI 1·53 to 6·21). Adjustment for concurrent atherosclerotic disease reduced the odds ratio to 2·63 (95% CI 1·26 to 5·45). The risk of aortic aneurysm was not related to elevation in diastolic blood pressure or in serum cholesterol.

Conclusions These findings indicate that atherosclerotic disease is associated with risk of aortic aneurysm in the general population. In addition, cigarette smoking appears to have a direct effect on the risk of aortic aneurysm which is independent of atherosclerosis.
(**Eur Heart J 1997; 18: 671–676**)

Key Words: Atherosclerosis, abdominal aortic aneurysm, cigarette smoking, cardiovascular risk factors.

Introduction

The presence of atherosclerotic changes in the aortic wall may be involved in the pathogenesis of abdominal aortic aneurysm. In support of this, numerous studies have shown an association between cardiovascular risk factors and aortic aneurysm[1–5]. In particular, a strong association between cigarette smoking and aortic aneurysm has long been recognised[6–8], although exactly which component of tobacco smoke is responsible for the increased risk remains uncertain. Hypertension has also been related to aortic aneurysm in previous studies[1,2,5,9,10]. Further support comes from observations during operations on aortic aneurysms and from autopsy studies which have shown calcified atherosclerotic degeneration in the walls of the aneurysm and raised lesions across the surface of the aneurysm[11,12]. However, the results of epidemiological, biochemical and genetic studies have implicated other aetiological factors suggesting a secondary role for atherosclerosis[8,12–19].

Using data from the Edinburgh Artery Study, we have assessed the relationship between various indicators of atherosclerotic disease and the risk of abdominal aortic aneurysm. In addition, we wished to identify which cardiovascular risk factors were related to the occurrence of aortic aneurysm. Furthermore, could such associations be fully explained by underlying atherosclerotic disease or were non-atherosclerotic processes implicated?

Methods

Study design

The study was carried out using subjects from the Edinburgh Artery Study which is a population-based cohort study comprising a baseline survey and follow-up over a period of 5 years. The present study design consisted of a nested case-control study in which cases were identified during the follow-up period and related to risk factors and other characteristics measured at baseline.

Baseline survey

During the baseline examination, 1592 subjects (809 men and 783 women) aged 55 to 74 years were recruited to the Edinburgh Artery Study. They were selected from the age/sex registers of 10 general practices with catchment populations spread geographically and socio-economically throughout the city of Edinburgh. Subjects attended a University clinic where they completed an extensive questionnaire, had a comprehensive medical examination and had a 12 lead electrocardiogram (ECG) performed. The questionnaire included the World Health Organisation (WHO) angina and intermittent claudication questionnaires and questions on medical and smoking history. Brachial systolic and diastolic (Phase V) blood pressure were measured in the right arm using a Hawksley random zero sphygmomanometer with the subject lying supine after a 10-min rest. Ankle systolic pressures were measured on the right and left legs with a Doppler probe and a random zero sphygmomanometer. A reactive hyperaemia test was carried out in which the ankle systolic pressure was measured in both legs 15 s after the release of a cuff occluding arterial flow for 4 min above the knee at 50 mmHg higher than systolic pressure. Standing height was measured without shoes to the nearest 5 mm with a free standing metal rule on a heavy base. Weight was measured without shoes and outer clothing to the nearest 100 g on digital scales (Soehnle).

From a fasting blood sample, total cholesterol, HDL cholesterol and triglycerides were estimated on a Cobas Bio analyser using standard kits. Complete details of the study population, recruitment and prevalence of disease have been described elsewhere[20].

Follow-up

During the 5-year follow-up period, information was obtained about non-fatal cardiovascular events including myocardial infarction, angina, stroke, transient ischaemic attacks and intermittent claudication. Criteria to define these events were adapted from those proposed by the American Heart Association[21]. The sources of such information were general practitioners, hospitals and the Information Services Division of the Scottish Home and Health Department. Also, each participant was sent an annual questionnaire enquiring about new medical conditions, hospital attendances and visits to their general practitioners in the previous year. Finally, each subject's record was flagged at the United Kingdom National Health Service Central Registry which ensured that any death certificates would be sent to us. All cardiovascular deaths and possible non-fatal events were further investigated using general practitioner or hospital records to ensure that the protocol criteria were fulfilled. Full details of these criteria have been documented[22].

Subjects had a 5-year follow-up examination between November 1992 and March 1994. A total of

1156 (72·6%) subjects attended for this second examination and completed a self-administered questionnaire, and a further 131 (8·2%) subjects completed the questionnaire only. In addition, there were 203 (12·8%) deaths making a total of 1490 (93·6%) subjects who were almost completely followed up. As part of the follow-up examination, an ultrasound scan of the abdomen was performed using a 3 MHz transducer and an ATL UM9 HDI system. For those unable to attend the clinic, an Aloka 500 Ultrasound Scanner (portable) was used to scan the abdomen during a home visit. All abdomen scans performed during a clinic visit were recorded on video. An aortic aneurysm was defined as a maximum anterior–posterior aortic diameter in systole of 30 mm or larger.

The videos from such subjects were checked by a consultant radiologist. After verification of an aortic aneurysm, the patient's general practitioner was informed and given information regarding management policy for asymptomatic aortic aneurysms in the Royal Infirmary of Edinburgh. In addition, subjects who were found to have an aortic aneurysm were counselled by the clinic staff.

During the follow-up examination, a total of 34 subjects were found to have an abdominal aortic aneurysm (mean size 4·2 cm, range 3·1 to 7·6 cm). In addition, three more subjects were found to have abdominal aortic aneurysm noted as a cause of death on their death certificate and a further three had been admitted to hospital with an abdominal aortic aneurysm during the follow-up period. Thus, a total of 40 cases of aneurysm were identified and for each, five controls were randomly selected from the remaining 1552 participants of the baseline survey matched by sex and within 5-year age group.

Statistical analysis

Data were analysed on the University of Edinburgh mainframe computer using SPSS-X and SAS. The distribution of triglycerides was highly skewed and so a logarithmic transformation was used in the analysis. Cigarette smoking status was classified into two groups: (1) current smokers plus ex-smokers who gave up within the last 5 years and (2) ex-smokers who gave up smoking more than 5 years ago plus never smokers. As a measure of lifetime cigarette smoking, the number of years smoked multiplied by the average number of packs smoked per day (packyears) was calculated. Nine subjects (one case and eight controls) were excluded from the packyears calculation because they currently or used to smoke a pipe or cigars, but had never smoked cigarettes. The distribution of packyears was skewed with a few heavy smokers and so a square root transformation was used. Body mass index was calculated as weight divided by the square of height (kg . m^{-2}). Hypertension was defined using WHO criteria (systolic >160 or diastolic >95) and compared with normotensives (systolic ≤160 and diastolic ≤95).

Table 1 **Demographic characteristics and cardiovascular risk factors at baseline in cases of abdominal aortic aneurysm and controls**

	Cases (n=40)	Controls (n=200)	P-value
Male	82·5	82·5	
Age (years)			
55–59	12·5	12·5	
60–64	17·5	17·5	
65–69	32·5	32·5	
70–74	37·5	37·5	
Current/recent ex-cigarette smokers	57·5	30·5	0·001
Packyears ($\sqrt{}$ among smokers)	5·58 (0·26)	4·76 (0·17)	0·025
Systolic blood pressure (mmHg)	149·8 (4·1)	146·7 (1·7)	0·469
Diastolic blood pressure (mmHg)	81·1 (2·5)	77·6 (0·9)	0·127
Hypertension†	25·0	25·5	0·947
Total cholesterol (mmol . l^{-1})	7·11 (0·22)	6·78 (0·9)	0·153
HDL cholesterol (mmol . l^{-1})	1·25 (0·06)	1·31 (0·03)	0·300
Triglycerides‡ (mmol . l^{-1})	1·53 (1·37, 1·71)	1·44 (1·34, 1 54)	0·444
Body mass index (kg . m^{-2})	25·31 (0·47)	25·35 (0·23)	0·942

Figures are percentage or mean (SE).
†Systolic >160 or diastolic >95.
‡Geometric mean (95% confidence interval).

The ankle brachial pressure index (ABPI) was calculated for each leg by dividing the ankle systolic pressure by the brachial systolic pressure. The lower of the indices between each leg was used as a continuous measure of cardiovascular disease in subsequent analysis. During the baseline survey, various measures of cardiovascular disease were obtained including WHO evidence of angina and intermittent claudication, ECG evidence of ischaemia and previous myocardial infarction, recall of a doctor diagnosis of angina and myocardial infarction, the ABPI and the reactive hyperaemia test. In the multivariate analysis, a discrete variable denoting cardiovascular disease was defined as any one of the following: myocardial infarction (any two of recall, WHO evidence or ECG); angina (any two of recall, WHO evidence or ECG); claudication (WHO evidence); major asymptomatic peripheral arterial disease (ABPI ≤0·9 and drop in ankle pressure during reactive hyperaemia >20% or ABPI ≤0·7 or reactive hyperaemia >35%).

Overall differences of risk factors between cases and controls were assessed using Student's t-test for the continuous factors and chi-squared analysis for the categorical factors. Various indicators of cardiovascular disease (myocardial infarction, angina and peripheral arterial disease) were examined to compare concurrent atherosclerosis in the cases and the controls. Age and sex adjusted odds ratios for aortic aneurysm were calculated for any factor which had shown a marked difference between cases and controls on univariate analysis. The odds ratios were first adjusted for age and sex because the cases and controls were frequency matched[23]. To determine if these factors were related to the risk of aortic aneurysm independently of the extent of atherosclerotic disease, the odds ratios were further adjusted simultaneously for the discrete variable cardiovascular disease and the ABPI.

Results

The 40 aneurysm cases comprised 33 (82·5%) males and seven (17·5%) females. The risk factor characteristics of the cases and controls are shown in Table 1. Age and sex were identical in cases and controls confirming the adequacy of the matching. Cases had higher serum total cholesterol and triglyceride levels and lower HDL cholesterol levels than did the controls, although the differences were not statistically significant ($P>0·05$). Similarly, cases had slightly higher systolic and diastolic blood pressure levels than controls ($P>0·05$). The proportion of defined hypertensives was almost identical in the two groups (25% of cases versus 25·5% of controls, $P>0·05$). This was not simply due to more of the cases taking medication to lower blood pressure since, at baseline, this was not significantly different between the two groups (12·5% of cases and 14% of controls, $P>0·05$). More of the aneurysm group were current or recent ex-cigarette smokers (gave up 5 years ago or less) ($P≤0·001$), with only three (7·5%) of them compared to 53 (26·5%) of the controls saying that they had never smoked cigarettes. In addition, the cases had a significantly higher lifetime cigarette smoking consumption than did the controls ($P≤0·05$). Body mass index was almost identical between cases and controls.

The presence of atherosclerotic disease in the cases and controls is shown in Table 2. Cases had a higher prevalence of myocardial infarction and angina, although neither difference reached statistical significance ($P>0·05$). For markers of peripheral arterial disease, more cases had intermittent claudication and evidence of major asymptomatic disease ($P≤0·001$). Using the combined definition of cardiovascular disease, the cases showed a significantly higher prevalence than the controls ($P≤0·05$). Finally, the cases had a significantly lower mean ABPI than the control group

Table 2   Cardiovascular disease at baseline in cases of abdominal aortic aneurysm and controls

	Cases (n=40)	Controls (n=200)	P-value
Myocardial infarction (any two of WHO evidence, recall and ECG changes†)	10·0	6·5	0·469*
Angina (any two of WHO evidence, recall and ECG changes‡)	22·5	18·0	0 506
Peripheral arterial disease (WHO defined claudicant or major asymptomatic disease)	35·0	13·0	0·001
Cardiovascular disease§ (any of the above)	50·0	32·0	0·029
Ankle brachial pressure index	0·93 (0·03)	1·03 (0·02)	0·007

Values are percentage or mean (SE).
†ECG codes for myocardial infarction were 1·1·1–1·2·5; 1·2·7; or 9·2 plus 5·1 or 5·2.
‡ECG codes for ischaemia were 1·3; 4·1–4 4; 5·1–5·3; 7·1.
§This definition is used in subsequent analysis.
*This P-value is derived using Fishers exact test.

Table 3   Logistic regression of cigarette smoking, diastolic blood pressure and total cholesterol on risk of abdominal aortic aneurysm

	Odds ratio of aneurysm (95% confidence interval)	
	Adjusted for age and sex	Adjusted for age, sex and atherosclerotic disease†
Cigarette smoking (current and ex ≤5 years ago versus ex >5 years ago and never)	3·08 (1·53, 6·21)**	2 63 (1·26, 5·45)**
Diastolic blood pressure (+5 mmHg)	1·10 (0·97, 1·24)	1·10 (0·98, 1·26)
Total cholesterol (+1 mmol . l⁻¹)	1·22 (0·94, 1·59)	1·17 (0·90, 1·53)

†Presence of cardiovascular disease at baseline and ankle brachial pressure index.
**$P \leq 0.01$.

($P \leq 0.01$) indicating more severe atherosclerotic disease among subjects with an aneurysm.

Table 3 shows the results of a logistic regression analysis of cigarette smoking, diastolic blood pressure and total cholesterol on aortic aneurysm and the extent to which these risks were independent of the presence of atherosclerotic disease. After adjustment for age and sex, current or recent ex-cigarette smokers had over three times the risk of having an aortic aneurysm than did ex-smokers who gave up more than 5 years ago and never smokers (odds ratio 3·08, 95% CI 1·53 to 6·21, $P \leq 0.01$). After further adjustment for atherosclerotic disease, the size of the odds ratio was reduced to 2·63 (95% CI 1·26 to 5·45, $P \leq 0.01$). A given unit increase (5 mmHg) in diastolic blood pressure did not significantly increase the risk of aortic aneurysm (odds ratio 1·10, 95% CI 0·97 to 1·24, $P > 0.05$) after controlling for age and sex. Further adjustment for atherosclerotic disease had a negligible effect. There was no statistically

significant increase in risk of aneurysm for a unit change (1 mmol . l⁻¹) in total cholesterol (odds ratio 1·22, 95% CI 0·94 to 1·59, $P > 0.05$) and further adjustment for underlying atherosclerosis had little effect.

Discussion

For many years, it has been generally accepted that the occurrence of abdominal aortic aneurysm is related to the presence of severe atherosclerosis of the aorta. However, observations such as the rarity of aneurysm formation in experimental atherosclerosis and the absence of atherosclerotic plaques in many subjects with aortic aneurysm suggest that aneurysmal disease may have different genetic and biochemical pathways than occlusive disease[8,12–14,16]. The principal aims of the present study were to examine the relationship between indicators of atherosclerotic disease and occurrence of

aneurysm. In addition, we wished to identify which of the common risk factors were associated with the risk of an aneurysm and whether the strength of this relationship was maintained after taking into account the presence of concurrent atherosclerotic disease. We found that significantly more of the aneurysm group had a history of cardiovascular disease than the controls. In addition, cigarette smoking was significantly associated with occurrence of an aneurysm. Adjusting for the presence of pre-existing cardiovascular disease and for the extent of atherosclerosis in the lower limbs (using the ankle brachial pressure index) made little difference to the magnitude of this increased risk. The results indicate that atherosclerosis is a contributing factor in the pathogenesis of aortic aneurysm. In addition, there is evidence of a direct effect of cigarette smoking on the risk of aortic aneurysm via pathways which are non-atherosclerotic in nature.

Several clinical studies have reported a high frequency of coronary and peripheral arterial disease among subjects with aortic aneurysm[4,24]. Likewise, in an autopsy study, coronary artery disease was found to be related to aneurysm formation[25]. An association has been observed between aneurysm and presence of angina[26], although we did not find a statistically significant relationship in our study. However, we did find some evidence of an association between the occurrence of an aneurysm and indicators of peripheral arterial disease. In particular, significantly more of the aneurysm group had intermittent claudication or major asymptomatic peripheral arterial disease and had a lower ABPI than did the control group. Ideally, the relationship between the presence of atherosclerotic disease and development of aortic aneurysm should be investigated in prospective studies, although such studies are few. One of them reported a relationship between cigarette smoking, hypertension, obesity and physical inactivity and the death rate from aortic aneurysm in the 6 year follow-up of a large population study[8]. Similarly, data from the prospective phase of the Honolulu Heart Program showed that high blood pressure, high serum cholesterol and cigarette smoking were predictors of aortic aneurysms identified at autopsy[12]. Furthermore, these predictors of aneurysm were identical to those that predicted aortic atherosclerosis in the same cohort.

Cigarette smoking has been shown to be one of the strongest risk factors for aneurysm formation and resultant death[5–8,26–28]. In addition, serum cotinine, a nicotine metabolite, has been correlated with aneurysm growth rate. Likewise, subjects who continue to smoke compared to those who stop smoking have higher aneurysm growth rates[29]. Furthermore, smoking appears to be a more potent risk factor for death from aneurysm than for death from coronary atherosclerosis[5]. In the present study, we found that the subjects with an aneurysm were more likely to be either current smokers or recent ex-smokers and had a significantly longer lifetime smoking history. After adjusting for age and sex, these subjects had over three times the risk of aneurysm than the combined group of those who gave

up smoking more than 5 years ago or who had never smoked cigarettes. Since smoking is reported to be the strongest risk factor for abdominal aortic aneurysm and is also associated with increased atherosclerosis, some degree of causality probably does exist. However, our finding that smoking maintained the strength of its association with aneurysm independently of the extent of atherosclerosis suggests an additional non-atherosclerotic pathway along which cigarette smoking acts. One explanation is that smoking constituents may block the active site of a_1-antitrypsin which could promote the destruction of the aortic wall by proteolytic enzymes[30]. In addition, other factors such as copper metabolism and tissue antioxidant levels may be involved in determining which smokers develop aneurysms independently of atherosclerotic obstruction[15,31].

Hypertension is an established risk factor for aneurysm formation and rupture[10,26,28]. In addition, diastolic blood pressure has been reported to show a stronger relationship with the presence of aneurysm than systolic blood pressure[2,5]. However, it is not known whether hypertension is involved in the pathogenesis of aneurysms directly or indirectly. A direct effect may arise from raised blood pressure increasing wall tension which, in turn, increases haemodynamic stress. This would exacerbate the effects of pre-existing weaknesses in the aortic wall leading to aneurysm formation. Alternatively, hypertension may have a role in explaining the increased frequency of atherosclerotic lesions seen in the abdominal aorta and lower limb arteries. These arise since the pressure in the abdominal aorta and its distal branches is higher than in the thoracic aorta. This increased intraluminal pressure may alter the endothelial permeability to serum lipid components. However, in the present study, we noted that neither blood pressure, nor presence of hypertension was significantly related to the risk of aortic aneurysm. Furthermore, this lack of an effect was not due to more of the cases taking blood pressure lowering drugs which would have particular relevance to aneurysm formation and dilatation[32].

Although the subjects with an aneurysm had a poorer lipid profile than the controls in our study, the differences were not statistically significant. Furthermore, none of the lipids were independently related to an increased risk of aneurysm with or without adjustment for underlying cardiovascular disease. This may be partly due to the small number of subjects with an aneurysm in this study. However, this lack of a lipid effect does support some previous reports[1,2,5,26,28], but is in contradiction to others[4,12,27].

Family studies have indicated that genetic factors seem to be important in the pathogenesis of aortic aneurysm[4,14,17,19]. Mechanisms may include increases in the enzymes responsible for the destruction of the aortic wall and direct inherited defects in elastin and/or collagen production. Further work, however, is needed to distinguish the precise mode of inheritance of aortic aneurysms. Although we currently have no genetic information on our subjects with an aneurysm, such analysis is planned for the near future.

A brief mention should be made about the limitations of the nested case-control design used in the present study. Since the abdominal scans were only performed at the follow-up examination, we have no data on how many of the subjects had an aneurysm at baseline and, therefore, we cannot measure incidence. Care should be taken in drawing inferences from the results since, with such a design, we are unable to separate cause and effect. Nonetheless, the findings are useful in generating areas for further research in future prospective studies.

The aetiology of abdominal aortic aneurysm is still not well understood, although the results of the present study provide further confirmatory evidence from a population-based study that atherosclerosis is a probable contributing factor. In addition, cigarette smoking appears to have an effect independently of atherosclerosis. More research is needed to elucidate the pathways involved in the role of cigarette smoking, although it is likely that a combination of both its atherosclerotic and non-atherosclerotic effects determine an increased susceptibility to aneurysm.

References

[1] Cronenwett JL, Murphy TF, Zelenock GB et al. Actuarial analysis of variables associated with rupture of small abdominal aortic aneurysms. Surgery 1985; 98: 472–82.

[2] Louwrens HD, Adamson J, Powell JT, Greenhalgh RM. Risk factors for atherosclerosis in men with stenosing or aneurysmal disease of the abdominal aorta. Int Angiol 1993; 12: 21–4.

[3] MacSweeney STR, Powell JT, Greenhalgh RM. Pathogenesis of abdominal aortic aneurysm. Br J Surg 1994; 81: 935–41.

[4] Norrgård Ö, Ängquist K-A, Johnson O. Familial aortic aneurysms: serum concentrations of triglyceride, cholesterol, HDL-cholesterol and (VLDL+LDL)-cholesterol. Br J Surg 1985; 72: 113–16.

[5] Strachan DP. Predictors of death from aortic aneurysm among middle-aged men: the Whitehall study. Br J Surg 1991; 78: 401–4.

[6] Auerbach O, Garfinkel L. Atherosclerosis and aneurysm of aorta in relation to smoking habits and age. Chest 1980; 78: 805–9.

[7] Doll R, Peto R. Mortality in relation to smoking: 20 years' observation on male British doctors. BMJ 1976; 2: 1525–36.

[8] Hammond EC, Garfinkel L. Coronary heart disease, stroke, and aortic aneurysm. Factors in the etiology. Arch Environ Health 1969; 19: 167–82.

[9] Gore I, Hirst AE. Arteriosclerotic aneurysms of the abdominal aorta. Prog Cardiovasc Dis 1973; 16: 113–50.

[10] Spittell JA. Hypertension and arterial aneurysm. J Am Coll Cardiol 1983; 1: 533–40.

[11] Dobrin P. Pathophysiology and pathogenesis of aortic aneurysms. Surg Clin North Am 1989, 69: 687–703.

[12] Reed D, Reed C, Stemmermann G, Hayashi T. Are aortic aneurysms caused by atherosclerosis? Circulation 1992; 85: 205–11.

[13] Busuttil RW, Abou-Zamzam AM, Machleder HI. Collagenase activity of the human aorta: A comparison of patients with and without abdominal aortic aneurysms Arch Surg 1980; 115: 1373–8.

[14] Clifton MA. Familial abdominal aortic aneurysms. Br J Surg 1977; 64: 765–6.

[15] Dobrin P, Baker W, Gley W. Elastolytic and collagenolytic studies of arteries. Arch Surg 1984; 119: 405–9.

[16] Powell JT, Greenhalgh RM. Multifactorial inheritance of abdominal aortic aneurysm. Eur J Vasc Surg 1987; 1: 29–31.

[17] Powell JT, Greenhalgh RM. Cellular, enzymatic and genetic factors in the pathogenesis of abdominal aortic aneurysm. J Vasc Surg 1989; 9: 297–304

[18] Tilson MD. Decreased hepatic copper levels: a possible chemical marker for the pathogenesis of aortic aneurysms in man. Arch Surg 1982; 117: 1212–13.

[19] Webster MW, St Jean PL, Steed DL, Ferrell RE, Majumder PP Abdominal aortic aneurysm: results of a family study. J Vasc Surg 1991: 13: 366–72.

[20] Fowkes FGR, Housley E, Cawood EHH et al. Edinburgh Artery Study. prevalence of asymptomatic and symptomatic peripheral arterial disease in the general population. Int J Epidemiol 1991; 20: 384–91.

[21] Gillum RF, Fortmann SP, Prineas RJ, Kottke TE. International diagnostic criteria for acute myocardial infarction and acute stroke. Am Heart J 1984; 108: 150–8.

[22] Leng GC, Lee AJ, Fowkes FGR et al. Incidence, natural history and cardiovascular events in symptomatic and asymptomatic peripheral arterial disease in the general population. Int J Epidemiol 1996; 25: 1172–81.

[23] Schlesselman JJ. Case Control Studies. Design, Conduct, Analysis. Oxford University Press, New York, 1982.

[24] Collin J, Araujo L, Walton J, Lindsell D. Oxford screening programme for abdominal aortic aneurysm in men aged 65 to 74 years. Lancet 1988; 2: 613–15.

[25] Bergqvist D, Bengtsson H, Sternby NH. Associated atherosclerotic manifestations. In Greenhalgh RM, Mannick JA, Powell JT, eds. The Cause and Management of Aneurysms. London: WB Saunders Company, 1990.

[26] Bengtsson H, Bergqvist D, Ekberg O, Janzon L. A population based screening of abdominal aortic aneurysm (AAA). Eur J Vasc Surg 1991; 5: 53–7.

[27] Pleumeekers HJCM, Hoes AW, van der Does E, van Urk H, de Jong PTVM, Grobbee DE. Aneurysms of the abdominal aorta in older adults The Rotterdam Study. Am J Epidemiol 1995; 142: 1291–9.

[28] Krohn FR, Kullmann G, Kvernebo K, Rosén L, Kroese A. Ultrasonographic screening for abdominal aortic aneurysm. Eur J Surg 1992; 158: 527–30.

[29] MacSweeney STR, Ellis M, Worrell PC, Greenhalgh RM, Powell JT. Smoking and the growth rate of small abdominal aortic aneurysms. Lancet 1994; 344: 651–2.

[30] Cohen JR, Sarfati I, Ratner L, Tilson MD. Alpha-1 antitrypsin phenotypes in patients with abdominal aortic aneurysms. J Surg Res 1990; 49: 319–21.

[31] Cannon J, Casteel L, Read RC. Abdominal aortic aneurysm, Lerich's syndrome, inguinal herniation, and smoking. Arch Surg 1984; 119: 387–9.

[32] Leach SD, Toole AL, Stern H, DeNatale RW, Tilson MD. Effect of beta-adrenergic blockade on the growth rate of abdominal aortic aneurysms. Arch Surg 1988; 123: 606–9.