

Risk factors for asymptomatic abdominal aortic aneurysm

Systematic review and meta-analysis of population-based screening studies

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Background: The incidence of and mortality from ruptured abdominal aortic aneurysm (AAA) is increasing. There is uncertainty regarding the indicators which could be used to identify groups at high risk. This issue has been addressed in a systematic review of population-based screening studies. **Methods:** MEDLINE and EMBASE were searched, reference lists scanned and manual searches made of eight journals. The search was restricted to four languages (English, German, French and Italian). Population-based studies investigating risk factors associated with screening-detected AAA were included. The following risk factors were considered: sex, smoking, hypertension, diabetes, a history myocardial infarction, and peripheral vascular disease. **Results:** Fourteen cross-sectional studies met our inclusion criteria. Most studies screened people aged 60 years or older. The prevalence of AAA ranged from 4.1% to 14.2% in men and from 0.35% to 6.2% in women. Male sex showed a strong association with AAA (OR 5.69), whereas smoking (OR 2.41), a history of myocardial infarction (OR 2.28) or peripheral vascular disease (OR 2.50) showed moderate associations. Hypertension was only weakly associated with AAA (OR 1.33) and no association was evident with diabetes (OR 1.02). **Conclusions:** The efficacy of screening men aged 60 years or older and women of the same age who smoke or have a history of peripheral or coronary artery disease should be evaluated in randomized controlled trials.

Keywords: abdominal, aortic aneurysm, cardiovascular diseases, mass screening

Abdominal aortic aneurysm (AAA) is defined as a permanent dilatation of the abdominal aorta. AAA usually remains asymptomatic unless it ruptures; a catastrophic event which is associated with high mortality rate, even in situations when time permits emergency surgery.¹ The aetiology of AAA is not fully understood but atherosclerosis, degenerative changes of the media with alterations in elastin and collagen, and chronic inflammation have been identified as contributing to its pathogenesis.^{2,3}

AAA appears to meet many of the classic criteria⁴ of screening for disease. First, AAA is an important health problem. In cross-sectional studies the prevalence varies according to the definition of AAA and the setting, with prevalences ranging from 3% to 8%.⁵ The incidence of asymptomatic AAA has increased in several countries during the last decades. For example, a national study from Denmark reported an increase in the incidence of asymptomatic lesions from 7.1 per 100,000 to 25.8 per 100,000 person-years.⁶ This trend could be explained by case-finding resulting from increased use of ultrasonography. However, the incidence of ruptured AAA and of age-standardized mortality also increased, indicating a real increase in the incidence of AAA. In the USA, the number of deaths attributed to AAA increased by almost 20% between 1979 and 1991. In 1991, 16,696 deaths were attributed to aortic aneurysm, abdominal aneurysm accounting for 52%.⁷ Secondly, abdominal ultrasound is a suitable test, which is non-invasive, relatively inexpensive and nearly 100% accurate in identifying the presence or absence of clinically relevant AAA.⁸ Thirdly, elective surgery is an effective treatment for patients with recognized disease. The mortality rate of elective surgery is

around 5%, but about ten times higher in emergency interventions.^{1,9} Since many patients die before reaching the hospital or before surgery can be arranged the mortality rate from ruptured AAA overall is 80% to 90%.¹ Finally, economic modelling suggests that screening may be cost-effective.¹⁰

The question whether screening for AAA should be introduced and who should be screened has been debated for some time.^{11,12} Authorities in the USA and Canada argued that there was insufficient evidence to recommend for or against routine screening of asymptomatic adults for AAA,^{13,14} whereas other authors recommended screening of high risk groups, such as current smokers.^{10,11} It is unclear, however, what risk factors could potentially be used to identify groups at high risk in whom screening might be cost-effective. We addressed this issue in a systematic review and meta-analysis of population-based screening studies.

METHODS

Literature search

We searched the MEDLINE and EMBASE databases using the following keywords and expressions in Ovid to identify relevant articles dealing with aortic aneurysm: 'aortic aneurysm, abdominal/'; 'aortic rupture/'; 'aorta, abdominal/'; 'exp aneurysm,ruptured/'; '(aortic adj5 aneurysm\$.tw.); '(abdominal adj5 dilatation).tw.'; '(abdominal adj5 aneurysm\$.tw.); '(thoracoabdominal adj5 aneurysm\$.tw.' These eight searches were combined with the Boolean 'OR' operator. Separate searches were performed to identify suitable study designs, using expressions 'exp cohort studies/'; 'exp risk/'; '(odds and ratio\$.tw.); '(relative and risk).tw.'; '(case and control\$.tw.'. The results from the search on aortic aneurysm was then combined with the search of relevant study designs. We complemented this search by scanning the reference lists of relevant articles and manual searches of *New England Journal of Medicine*, *The Lancet*, *Annals of Internal Medicine*, *Circulation*, *JAMA*, *American Journal of Public Health*, *BMJ*, *Journal of Medical Screening*, and *British Journal of Surgery*. We restricted our search to four languages (English, German, French and Italian) and to the period 1985 to 1998. We excluded earlier studies because

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ultrasound technology was not available before 1985. The search is described in detail elsewhere.¹⁵

Inclusion criteria

We included all original reports from population-based studies investigating factors associated with screening-detected AAA. Study populations identified from censuses, lists of health care providers, or from other membership lists were eligible. We excluded studies based on patients attending hospital or outpatient clinics and studies not providing a clear definition of AAA. Two of us (JC, CSP) independently performed a first selection of the retrieved articles on the basis of title and abstract. Inter-observer agreement was good ($\kappa=0.60$).¹⁶ Disagreement was resolved by consensus.

Data extraction

The following data were independently abstracted by two of us (JC, CSP): study design, setting, AAA screening method and definition of AAA, the number of people invited to be screened, the number screened, and the number with AAA. The number of study participants with and without risk factors in AAA and comparison groups, and definitions for risk factors were also extracted in duplicate. The following risk factors were considered: sex, smoking, hypertension, diabetes, a history myocardial infarction, and peripheral vascular disease. Inconsistencies in abstracted data were resolved by consensus.

Data synthesis and exploration of heterogeneity

We calculated the prevalence of AAA as the number of study participants with AAA divided by the number with successful ultrasound examinations. We determined prevalence separately for men and women whenever possible and calculated exact binomial 95% confidence intervals (CIs). Risk factor associations were expressed as odds ratios (ORs) to obtain consistency across studies. Only a few authors have performed multivariable analyses, and those who did included different sets of variables in their models. We therefore used crude odds ratios throughout. We combined studies both by DerSimonian and Laird random-effects and Mantel-Haenszel fixed-effects models.¹⁷ We calculated standard tests of homogeneity and explored sources of heterogeneity between studies using meta-regression models. Covariates considered included the year of publication, country (United Kingdom or other), whether the study included men only, and the prevalence of AAA found. The regression model of treatment effect on covariates used an overdispersion parameter (in the terminology of Thompson and Sharp¹⁸) to allow for residual heterogeneity between studies. We explored potential publication bias by examining the symmetry of funnel plots, using a regression approach.¹⁹ All analyses were done using the statistical package Stata version 6 (Stata Corporation, College Station, Texas, USA).

RESULTS

A total of 2238 articles were identified of which 185 (8.3%) were considered to be potentially relevant and assessed in detail. Eighteen articles (0.80%) from 14 studies met our inclusion criteria. *Figure 1* gives a schematic representation of the selection process and reasons for excluding studies. The characteristics of the 14 included studies are summarised in *table 1*. All studies were based on general population samples and used abdominal ultrasound as screening test. Nine enrolled people registered with general practices, health maintenance organisations, Medicare or Veterans Affairs medical centres, three were census based and one study enrolled customers of bowling clubs, shopping centres and residents of a retirement village. All studies were cross-sectional except for one²⁰ which included a cross-sectional study as well as was a case-control study. Four analyses were based on populations enrolled in cohort studies: The Men born in 1914

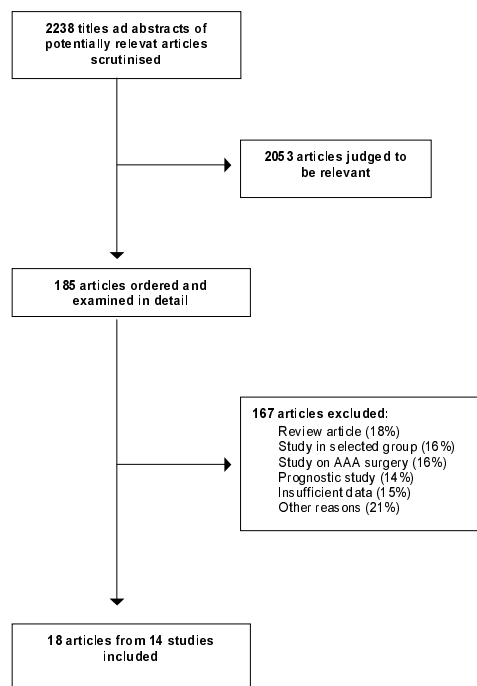


Figure 1 Flow chart showing progress in identification and selection of relevant studies

from Malmö cohort,²¹ the Rotterdam Study,²² the US Cardiovascular Health Study²³ and the Edinburgh Artery Study.²⁰ The proportion of those invited who attended screening ranged from 28.5% in the large US veterans study²⁴ to 84.2% in the Cardiovascular Health Study. The number of people screened ranged from 375 in the Swedish study²¹ to 73,451 in the US veterans study.²⁴

The definitions used for AAA varied between studies although seven of the 14 studies used a similar definition (a diameter greater than 28–30 mm) (*table 2*). The denominator in the calculation of prevalence was sometimes smaller than the total number screened because the aorta could not always be visualized. The study from Norway²⁵ reported on the first 500 study participants only. The prevalence of AAA ranged from 4.1% to 14.2% in men and from 0.35% to 6.2% in women.

The definitions used by authors for the different risk factors or risk indicators were also heterogeneous across studies (*table 3*). For example, some investigators relied on a history of claudication for the definition of peripheral vascular disease whereas others performed clinical examinations and calculated ankle brachial pressure indices. Some risk factors were examined in some studies but not in others. For example, data on smoking were reported in 11 studies whereas the importance of diabetes was examined in six studies only.

Figure 2 shows plots of odds ratios from individual studies and combined odds ratios from random-effects models and *table 4* gives combined odds ratios calculated by random and fixed-effects models and probabilities from tests of heterogeneity. Male sex showed the strongest association with AAA, whereas myocardial infarction, peripheral vascular disease and smoking showed moderate associations. Hypertension was only weakly associated with AAA and no association was evident with diabetes. There was significant heterogeneity between results from individual studies for male sex and smoking, and in these instances combined odds ratios from random-effects and fixed-effects differed to some extent. Meta-regression analyses indicate

Table 1 Characteristics of population-based studies of asymptomatic abdominal aortic aneurysm

Study	Setting	Inclusion criteria		Number invited	Number screened (%)
		Age (years)	Sex		
Oxford ⁴⁵	Two large group practices in Oxford, UK	65–74	Men	824	426 (51.7)
Gloucester ⁴⁶	Four group practices in Gloucester, UK	65–74	Men	1,195	906 (76.0)
Malmö ^{21,47}	Citizens of Malmö, Sweden born in even months in 1914	74	Men	499	375 (75.0)
Oslo ²⁵	Men registered with private Health Maintenance Organisation in Oslo, Norway	60–89	Men	2,674	1,246 (46.6)
Asola ⁴⁸	Residents of Asola, Italy	>60	Men and women	1,122	648 (57.1)
Freemantle ⁴⁹	Members of bowling clubs, clients of a shopping centre and retired residents from Freemantle, Australia	60–80	Men and women	Not reported	1,225 (–)
Birmingham ^{50,51}	Twenty-two general practices in Birmingham, UK	60–75	Men	13,000	10,061 (77.4)
Rotterdam ²²	Residents of Rotterdam, The Netherlands who participate in Rotterdam Study	≥55	Men and women	6,947	5,419 (78.0)
Genoa ^{52,53}	Twenty-six general practices in Genoa, Italy	65–75	Men and women	2,734	1,601 (58.5)
Chichester ^{39,54}	All general practices in Chichester health district, UK	65–80	Men and women	7887	5,394 (68.4)
Viborg ⁵⁵	Residents of Viborg county, Denmark	65–73	Men	4,404	3,344 (76.0)
USA Counties ²³	People on Medicare lists from four US Counties who participated in Cardiovascular Health Study	≥65	Men and women	5,629	4,741 (84.2)
Edinburgh ²⁰	People on practice lists of ten practices who participated in the Edinburgh Artery Study	55–74	Men and women	1,592	1,156 (72.6)
USA Veterans ²⁴	People registered with 15 Department of Veterans Affairs medical centers	50–79	Men and women	259,623	73,943 (28.5)

Table 2 Prevalence of asymptomatic abdominal aortic aneurysm in men and women

Study	Definition of AAA (diameter or infra- to supra-renal ratio [I/S])	Men		Women	
		Number of AAAs / Number successfully screened	Prevalence in per cent (95% CI)	Number of AAAs / Number successfully screened	Prevalence in per cent (95% CI)
Oxford	40 mm or I/S >1.5	23 / 426	5.4 (3.5–8.0)	n.a.	
Gloucester	>25 mm	71 / 906	7.8 (6.2–9.8)	n.a.	
Malmö	>35 mm	39 / 338	11.5 (8.3–15.4)	n.a.	
Oslo	≥30 mm or I/S >1.5	41 / 500	8.2 (5.9–11.0)	n.a.	
Asola	>25 mm	n.r. ^a		n.r. ^a	
Freemantle	>30 mm	31 / 654	4.7 (3.2–6.7)	2 / 571	0.35 (0.04–1.3)
Birmingham	≥29 mm	706 / 9771	7.2 (6.7–7.8)	n.a.	
Rotterdam	≥35 mm or I/S >1.5	91 / 2217	4.1 (3.3–5.0)	21 / 3066	0.68 (0.42–1.0)
Genoa	≥30 mm	65 / 741	8.8 (6.8–11.0)	5 / 860	0.58 (0.19–1.4)
Chichester	≥30 mm	178 / 2342	7.6 (6.6–8.7)	40 / 3052	1.3 (0.9–1.8)
Viborg	≥30 mm	141 / 3344	4.2 (3.6–4.9)	n.a.	
USA Counties	≥30 mm or I/S >1.2	278 / 1956	14.2 (12.7–15.8)	173 / 2785	6.2 (5.3–7.2)
Edinburgh	≥30 mm	n.r. ^b		n.r. ^b	
USA Veterans	≥30 mm	3298 / 71373	4.6 (4.5–4.8)	25 / 1885	1.3 (0.8–1.8)

a: Sex-specific prevalence not reported. There were 20 AAAs among 354 men and 294 women, for a prevalence overall of 3.1% (95% CI: 1.9–4.7).

b: Sex-specific prevalence not reported. There were 34 AAAs among 1156 men and women, for a prevalence overall of 2.9% (95% CI: 2.0–4.1).

AAA: asymptomatic abdominal aneurysm

95% CI: 95% confidence interval

n.a.: not applicable; n.r.: no data, or no data in appropriate format reported.

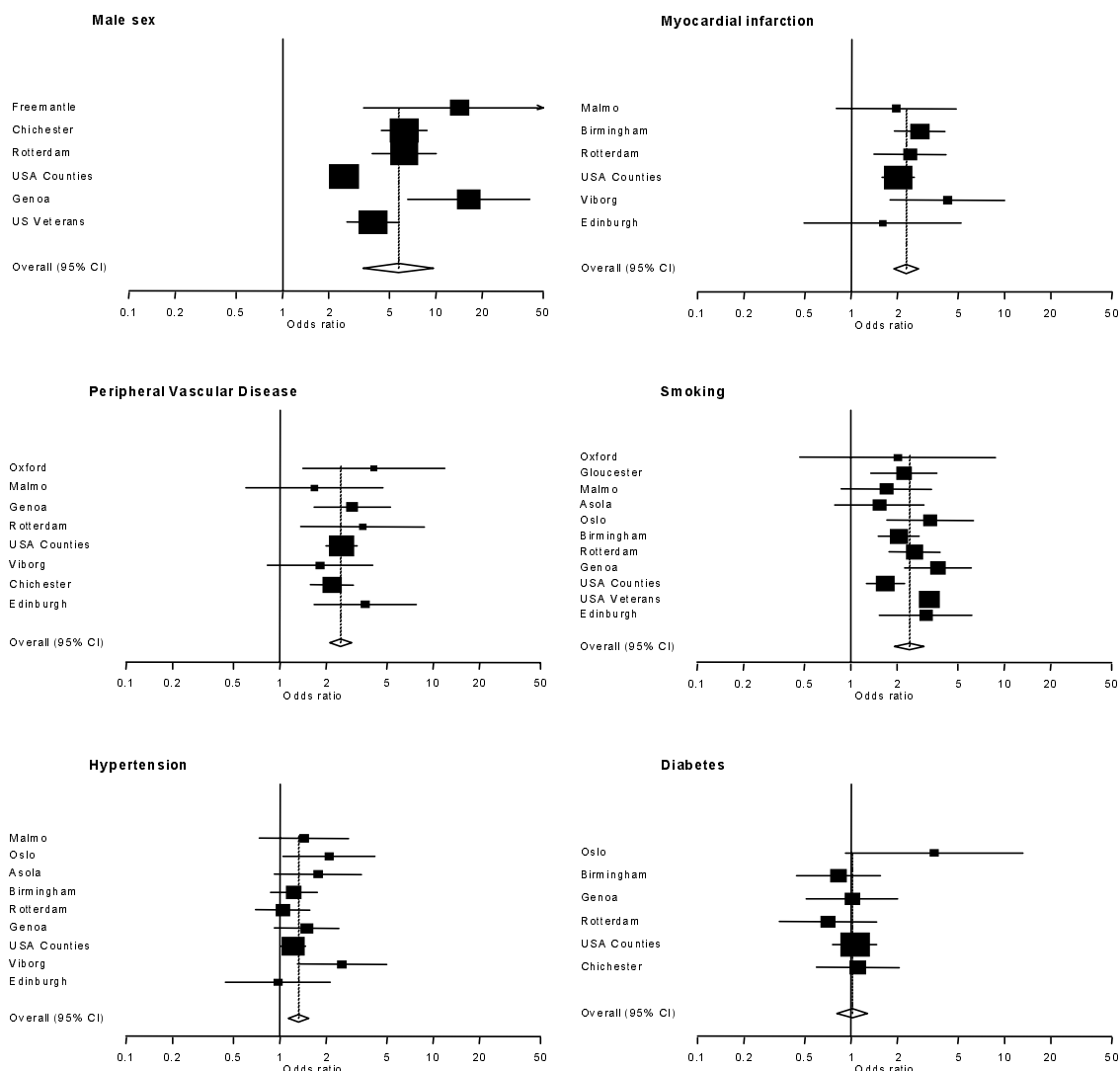


Figure 2 Forest plot of studies of risk factors for abdominal aortic aneurysm. Black squares indicate odds ratios and 95% confidence intervals from individual studies and diamonds combined odds ratios and 95% confidence intervals from random-effects models. The size of the black squares are proportional to the weight of the study in the analysis.

that both for male sex and smoking the prevalence of AAA explained the heterogeneous results: the lower the prevalence of AAA in a given study, the stronger the association between male sex and AAA and smoking and AAA. The models predicted that for a prevalence of AAA of 1% the odds ratio would be 8.63 for male sex and 3.84 for smoking. Conversely, for a prevalence of AAA of 10% the corresponding odds ratios would be 2.33 and 1.77. There was no evidence of publication bias.

DISCUSSION

To our knowledge this is the first systematic review and meta-analysis of population-based risk factor studies of AAA. The results show that male sex, current cigarette smoking, and a history of peripheral or coronary artery disease are all major risk factors or risk indicators for screening-detected AAA, with pooled odds ratios ranging from 2.3 to 5.7. Interestingly, hypertension appears to be only weakly associated with AAA and no association was found with diabetes. The population prevalence of AAA varied widely which is not surprising considering the differences between studies in terms of their definition of AAA, the age and sex distribution of study populations, and the prevalence of risk factors and pre-existing morbidity.

We focused on population-based screening studies and thus minimized detection, recall and interviewer bias. A spurious association between a risk factor and AAA will result if the presence or absence of this factor influences the probability of detecting an aneurysm. For example, if many doctors believe that patients with hypertension should be examined specifically then diagnostic suspicion bias may be introduced in studies in which case detection relies on routine clinical diagnosis or information from death certificates.⁵ The case ascertainment in the screening studies included in the present review was uniform within studies, according to standardized criteria. Furthermore, in most studies exposure information was collected before the diameter of the abdominal aorta became known, effectively eliminating interviewer and recall bias. Our literature search was comprehensive and covered different languages, which should have minimized reporting biases.²⁶ Finally, we examined possible sources of heterogeneity, and found that the underlying prevalence of AAA explained some between-study heterogeneity. This could reflect stronger risk factor associations, in relative terms, in younger study populations who have a lower prevalence of AAA, which is consistent with other cardiovascular conditions.²⁸ Alternatively, associations could be weaker because of a

broader, and less specific, definition of AAA in high prevalence studies.

Our study illustrates several difficulties of systematic reviews of observational studies.²⁷ In contrast to randomized controlled trials²⁹ there are no agreed quality criteria for assessing cross-sectional studies. Furthermore, we used unadjusted results throughout, which allowed us to compare consistent estimates across studies. However, these estimates may be biased in terms of the aetiological importance of different risk factors. Only few authors examined this issue in multivariable analyses. In the US veterans study,²⁴ the strength of the association of AAA with

male sex was attenuated when adjusting for smoking, a history of cardiovascular disease and a range of cardiovascular risk factors. We stress that our main objective was not to clarify the aetiology of AAA but to identify risk factors or indicators that may be useful to identify patients at increased risk in a screening context. Keeping this in mind is also important when interpreting the weak association with hypertension: prospective studies have shown that mortality from aortic aneurysm, particularly dissecting aneurysm, increases with blood pressure.³⁰ Hypertension may thus be a relatively poor predictor of the risk of asymptomatic AAA in the general population but at the same

Table 3 Definition of risk factors as described in original publications

Study	Myocardial infarction	Peripheral vascular disease	Smoking	Hypertension	Diabetes
Oxford	n.r.	History of claudication	Current and former vs. never smokers	n.r.	n.r.
Gloucester	n.r.	n.r.	Smokers vs. non smokers	n.r.	n.r.
Malmö	Medical history	ABPI <0.9	Smokers vs. non smokers	DBP >105 mmHg or antihypertensive treatment	n.r.
Oslo	n.r.	n.r.	Smokers vs. non smokers and former smokers	Antihypertensive treatment	Medical history
Asola	n.r.	n.r.	Smokers vs. non smokers and former smokers	Not defined	n.r.
Freemantle	n.r.	n.r.	n.r.	n.r.	n.r.
Birmingham	ECG or enzymes changes	n.r.	>10 cigarettes/day vs. others	SBP >160 mmHg or DBP >90 or antihypertensive treatment	Medical history
Rotterdam	Medical history	Rose questionnaire	Smokers vs. non smokers	SBP >160 mmHg or DBP >95 or antihypertensive treatment	Antidiabetic drug or glycemia >11 mmol/l
Genoa	n.r.	History of claudication	Smokers vs. non smokers	SBP >160 mmHg or DBP >90 mmHg or antihypertensive treatment	Medical history
Chichester	Medical history	n.r.	n.r.	n.r.	Medical history
Viborg	Not defined	Chart review	Smokers vs. non smokers	WHO definition	n.r.
USA Counties	Medical history	Rose questionnaire or ABPI <0.9	Smokers vs. non smokers	Antihypertensive treatment	Glycemia >11 mmol/l
Edinburgh	Medical history	ABPI ≤0.9 and drop in ankle pressure >20% or ABPI ≤0.7 or reactive hyperaemia >35%	Smokers and recent quitters (past 5 years) vs. others	SBP >160 mmHg or DBP >95 mmHg	n.r.
USA Veterans	n.r.	n.r.	Ever smokers of >100 cigarettes vs. others	n.r.	n.r.

ABPI: ankle brachial pressure index

SBP: systolic blood pressure

DBP: diastolic blood pressure

n.r.: no data, or no data in appropriate format reported.

Table 4 Combined odds ratios for the presence of asymptomatic abdominal aneurysm from meta-analysis

Risk factor	Number of studies	Combined odds ratio (95% CI)		p from test of heterogeneity
		Random-effects model	Fixed-effects model	
Sex (male vs. female)	6	5.69 (3.36–9.64)	3.96 (3.42–4.59)	<0.0001
History of myocardial infarction (yes vs. no)	6	2.28 (1.90–2.74)	2.30 (1.92–2.75)	0.47
Peripheral vascular disease (yes vs. no)	8	2.50 (2.12–2.95)	2.48 (2.10–2.92)	0.74
Smoking (yes vs. no)	11	2.41 (1.94–3.01)	2.89 (2.63–3.16)	0.001
Hypertension (yes vs. no)	9	1.33 (1.14–1.55)	1.31 (1.14–1.49)	0.34
Diabetes (yes vs. no)	6	1.02 (0.81–1.29)	1.00 (0.80–1.26)	0.44

time be an important risk factor for rupture in patients with AAA.

Our review has other limitations. We did not consider a number of variables, including age, race and lipid factors, because only few studies reported relevant data. The strong association of AAA with age is, however, well established both for men and women. Epidemiological necropsy^{31,32} and screening studies²² documented a sharp increase in the prevalence of AAA after age 60, which in men reaches 6% to 9% and in women 2% to 3% by age 80. Two studies^{23,24} examined the importance of race and the study dominated by men,²⁴ but not the one dominated by women,²³ found that black race was negatively associated with AAA, in line with US mortality statistics that show racial differences for men but not women.⁷ Three studies²²⁻²⁴ examined lipid factors, but used different methods. In the USA Counties Study²³ the prevalence of AAA was increased among participants with HDL cholesterol levels below 40 mg/dl (1 mmol/l) and slightly increased if LDL cholesterol was above 160 mg/dl (4.2 mmol/l). The Rotterdam study²² examined total cholesterol and found only small differences whereas the results from the Veterans Affairs Cooperative Study²⁴ are difficult to interpret because analyses were based on inaccurate, self-reported cholesterol levels. The exact etiologic role of lipid factors thus remains unclear but they are likely to contribute to any atherosclerotic component of the pathogenesis of aortic aneurysms. Studies^{24,33,53} that examined the importance of a positive family history found that such a history increased the risk of AAA. Finally, all studies included in our review were cross-sectional which means that strictly speaking it is impossible to define the temporal sequence between exposures and aneurysm formation.

What are the implications for screening for AAA? First, our review shows that the numbers needed to screen (NNS)³⁴ to detect one patient with AAA are relatively low in the populations examined: the prevalences shown in table 3 translate to NNS of 7 to 24 in men and 16 to 286 in women, which compares favourably with other diseases for which routine screening is currently recommended, such as breast cancer^{35,36} or colorectal cancer.³⁷ This is, however, insufficient evidence to recommend screening for AAA. Most screening-detected aneurysms are small. The risk of rupture is low in these cases and the majority of patients will die from other causes, with their aneurysm intact.³⁸⁻⁴⁰ The UK Small Aneurysm Trial,⁹ which enrolled 1090 patients with aneurysms of 40 to 55 mm diameter found an operative mortality of 5.8% in patients allocated to early elective surgery and a risk of rupture for small aneurysms of only 1% per year in the group randomised to ultrasonographic surveillance. Early surgery conferred no long-term survival advantage but increased workload and costs for the health service.⁹ Regular ultrasonography, rather than surgery, is therefore recommended in smaller AAAs (diameters below 50 to 55 mm). Most surgeons agree that aneurysms exceeding 55 mm in diameter should be repaired if there are no concomitant conditions which would substantially increase the risk of elective surgery, such as severe cardiac or respiratory disease.

The NNS to prevent one death from ruptured AAA has recently been determined by the Multicentre Aneurysm Screening Study (MASS).^{41,42} This randomised controlled trial allocated 67,800 men aged 65 to 74 years to an invitation to undergo an abdominal ultrasound scan (with follow-up scans or immediate surgery if AAA was detected) or to a control group. In the intervention group, 80% of men accepted the invitation and over four years of follow-up AAA related mortality was reduced from 0.33% to 0.19% (risk reduction 42%, 95% confidence interval 22% to 64%).⁴¹ This means that 714 men need to be screened to prevent one death, which in economic evaluation⁴² was found to be only marginally cost-effective, although cost-effectiveness is expected to improve over a longer period of follow up. The

cost-effectiveness of screening programmes could be increased if screening was specifically targeted at the groups at high risk. One programme, for example, used a scoring system which allocated one point each for being male, diabetic, suffering from hypertension and having raised lipids.⁴³ Our findings indicate that a history of diabetes, hypertension and dyslipidaemia should not be used to identify people at increased risk of AAA. Targeted screening is of course efficient only if most events occur in readily defined subgroups of the population. Apart from being male our data do not suggest that there are risk factors that are sufficiently common and strong to form the basis of selective screening. A study from Australia⁴⁴ concluded that screening the 70% of men who had ever smoked would detect 87% of aneurysms, which represents only a marginal gain in efficiency. Selective screening may, however, have a role in female populations. Decision analysis and modelling based on our findings and those from randomized trials could help identify the most promising target groups and long-term screening strategies.

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