Factors Associated with Development of Large Abdominal Aortic Aneurysm in Middle-aged Men.

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Factors associated with development of large abdominal aortic aneurysm in middle-aged men.

Short title: Associated factors for development of AAA

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Abstract

We investigated whether any variables in a health-screened population study were associated with later development of large abdominal aortic aneurysms (AAA).

Setting: Malmö, southern Sweden.

Material and methods: Within the Malmö Preventive Study 22 444 men and 10 982 women were investigated between 1974 and 1991. The mean age at the health screening was 43.7 years.

Results: After a median follow-up of 21 years, 126 men and six women ($p<0.001$) had large AAA that were symptomatic or evaluated for operation (5 cm diameter or more) or had autopsy-verified ruptured AAA. The male group (mean age 47 years) was, because of difference in age ($p<0.001$,) also compared with an age-matched control group. The male patients with AAA showed increased diastolic blood pressure ($p<0.007$) at the health screening. Smoking predicted the development of AAA ($p<0.0001$). No difference in forced vital capacity or BMI was seen. Those who were physically inactive (e.g. not walking or cycling to work) had an increased risk of developing AAA ($p<0.001$). Among the laboratory markers measured, the erythrocyte sedimentation rate did not differ (7.1±5.9 vs. 6.4±5.7), but cholesterol (6.3±1.12 vs. 5.8±1.0) ($p<0.0001$) and triglycerides (1.9±0.12 vs. 1.5±0.07) ($p<0.001$) were significantly elevated in these individuals who subsequently developing AAA. The inflammatory proteins alfa-1-antitrypsin, ceruloplasmin, orosmucoid, fibrinogen, and haptoglobulin were increased ($p<0.001$).

Conclusion: After a logistic regression analysis, male gender, smoking, physical inactivity and cholesterol remained significant and were factors associated with the development of AAA during 21 years' follow-up. We established all risk factors, except for physical inactivity, that needs to be further verified.

Key words: AAA, associated risk factors, atherosclerosis, smoking, hypercholesterolemia, inflammatory markers.

Introduction

Abdominal aortic aneurysm (AAA) is relatively common in elderly men. Elastin and collagen degradation, increased activity of matrix metalloproteinases, inflammatory and immunologic activity, as well as altered wall shear stress, may be causative factors for the development of AAA [1]. There are few studies on factors associated with the development of AAA during long-time follow-up in apparently healthy individuals [2-3]. Most studies have analysed subpopulations or patients with confirmed AAA [4-10]. Previous studies have shown age, male gender, smoking, hypertension and high cholesterol levels to be associated with the development of AAA [2-10].

The evaluation of the incidence of AAA was previously based on autopsy findings, selected case studies, but also on population screening studies in which ultrasonography was used. In this study no initial screening for AAA was made and we included only those from our population cohort who had symptomatic AAA or AAA with a diameter larger than 5 cm and were evaluated for treatment or autopsy-proven ruptured AAA. The aim of this study was to further investigate whether the above-presented risk factors were associated also with later development of large AAA in a population-based cohort.

Material and Methods

The Malmö Prevention Project[11,12] is a health screening and intervention programme carried out during a 17-year period (1974-1991). A total of 22 444 men (mean age 43.7±7 years) participated (participation rate 71%), of whom 126 were found to develop AAA. The health screening programme also included a population of 10 982 women, but in this group only six individuals have been diagnosed with the development of AAA ($p<0.001$).

Health Screening Procedure

The health screening and examination procedures have previously been described in detail.[11, 12] In brief; heart rate and blood pressure (BP) were measured in the right arm after 10 minutes' rest. Body mass index (BMI) was calculated as kg/m^2. Diabetes mellitus was considered to be present, if there was a history of treatment of diabetes or a fasting blood glucose level of more than 6.7 mmol/l or equal. Smoking was defined as current smoking at the time of participation in the health screening programme. Forced vital lung capacity (FVC), measured with a Spiroton apparatus (Drägerwerk AG, Lübeck, Germany), and activity assessed from a questionnaire decided the measure of physical fitness. The use of blood pressure-lowering drugs, heart glycosides, nitro vasodilators and analgesic drugs was recorded.

Venous blood was collected after an overnight fast in order5 to determine the erythrocyte sedimentation rate (ESR), hematocrit and haemoglobin (Hb) levels, total leukocyte count, platelet count, and serum total cholesterol, triglycerides, total calcium, albumin, creatinine, electrolytes, gamma glutamic acid transferase (GT), alaninaminotrasanferase (ALAT), aspartataminotransferase (ASAT), alkalic phosphatases (ALP) and uric acid. The analyses were performed by routine methods at the Clinical Chemistry Laboratory of Malmö University Hospital. The fasting capillary blood glucose level was determined in all subjects.

Individuals who were health-screened and had hypertension, hyperlipidemia, diabetes mellitus or pathological glucose tolerance or high alcohol intake were offered intervention and referred to outpatient clinics.

The Ethics Committee at Lund University approved the study. All participants gave informed consent.

Patients and control groups

During the 28 years between the start of this health screening programme and December 31, 2002, 126 men and six women of this cohort were documented to have symptomatic or large (5-5.5 cm in diameter) AAA. They either underwent operative reconstruction (n=98), were evaluated for aneurysm exclusion, but treated conservatively (n=19), or were found to have autopsy-verified ruptured AAA (n=15). This documentation was based on hospital register data, SwedVasc quality control data and death certificates. Thus, only those who had objectively documented treatment-requiring AAA were included in the analysed group.

Plasma protein analyses were performed in a subgroup of 6 477 men of whom 63 developed AAA. Details have been separately reported [10], but are included to give as much information as possible on the factors associated with the development of AAA.

Male patient baseline values for the different variables at the time of health screening were compared with the corresponding values for the case control group established because of differences in age. The closest birth date case not having AAA was selected to the control group, but also to the entire screened male population cohort (n=22 444 [6 477 regarding plasma protein analyses]).

Statistics

Values are presented as mean ± SD. The differences between groups were assessed with the Mann-Whitney U test, or the Chi-squared test as appropriate. Because of the multiple comparisons, a post-hoc adjustment using Bonferroni's correction of p values was performed, revealing that only p values below 0.01 should be considered as truly significant.

The relative risk of the development of AAA was estimated in terms of the odds ratio (OR) and the 95-per cent confidence interval (CI) for a one standard deviation increase (for measurable variables) or in terms of the presence versus absence of a given factor as determined by a logistic regression analysis. The independent significance of each variable was assessed by a multiple logistic regression analysis after adjustment for other significant risk factors. In this analysis p values less than 0.05 were considered statistically significant.

Results

Six women and 126 men developed AAA during the observation period ($p<0.0001$). The median time between the health screening and detection of AAA was 21 years (range 6-30 years), and the median age at the detection of AAA was 68 years (range 49-81 years). Male patients with AAA (n=126) were further analysed. At the health screening, this group was significantly older (47[37-60] years) than the entire screened male population (n=22 444, 43.7[26-61] years; $p<0.0001$). Therefore, we established an age-adjusted case control group with 126 patients. Demographic data at health screening are seen in Table I. The male patients with AAA had higher diastolic blood pressure (134/90 mmHg versus 131/86 mmHg; $p<0.007$).

A significantly higher proportion of the patients with AAA were smokers at the health screening (81% versus 51%; $p<0.0001$). Those who had smoked daily for more than 10 years were even more frequent among the patients who developed AAA ($p<0.0001$). The subgroup of pipe smokers also seemed to have an increased risk ($p<0.08$).

We could not see reported alcohol consumption to be a risk of the development of AAA. Neither were factors as being busy, easily stressed, impatient or suffering from insomnia associated with later development of AAA. The initial questionnaire from the health screening showed that the case control group and entire male population were more physical active ($p<0.001$) than those who developed AAA. Forced vital capacity did, however, not differ.

Laboratory data (Table II) showed increased serum total cholesterol (6.3±1.1 mmol/l versus 5.9±1.0 mmol/l; $p<0.0001$), triglyceride (1.9±1.2 mmol/l versus 1.5±0.7 mmol/l; $p<0.0001$), and plasma fibrinogen levels in a subgroup (3.95±0.65 mmol/l versus 3.50±0.80 mmol/l; $p<0.001$, Table III) in subjects later developing AAA.

We did not find any differences regarding the recorded use of medication between the patients with AAA and the control group or the background health-screened population.

Furthermore, a logistic regression analysis was performed to evaluate the variables that differed as factors associated with later AAA. Smoking, physical inactivity, and serum cholesterol remained as independent associated factors (Table IV). Since fibrinogen was only analysed in a subgroup of 63 patients with AAA and 6 477 of the background

population, a separate logistic regression analysis was performed in this group in which fibrinogen was not an independent predictor (p=0.062).

There were no differences concerning the health screening variables between subjects operated on because of ruptured, symptomatic or asymptomatic AAA. Neither were there any significant differences concerning associated factors in the patients with AAA, with different time intervals between the health screening and the development of AAA below or above the median of 21 years after screening (data not shown).

The absolute risk of developing a large AAA during a 21-year follow-up of initially 47-year-old men was 0.56 per cent, which was increased among the smokers to 0.9 per cent (100 AAA among 11 403 smokers) compared with 0.2 per cent among the non-smokers (26 AAA among11 041 non-smokers). In Table V, we show the absolute risk of different quartiles of serum-total cholesterol. In the highest quartile, we saw an absolute risk of 1.2 per cent compared with 0.1 per cent in the lowest quartile of serum-total cholesterol values.

Discussion

In recent years, we have learned much about the etiopathology of the development of AAA. Some of the more important factors are elastolysis, impaired collagen production and increased degradation, increased levels of matrix proteinases, inflammatory reactions with increased CRP levels, leukocyte and macrophage accumulation in the aneurysmal wall, and increased immunological activity [1].

This study verifies earlier population-based studies showing several factors associated with the development of AAA such as male gender, smoking and high cholesterol levels [2-10]. In addition, a large number of case control studies on patients with AAA have focused on these risk factors, and an association has been further verified between AAA and age [4, 5, 7-9], male gender [4-10, 13-19], smoking [2-10, 13-17], total cholesterol [3, 5, 8-10] and suggested by several studies for hypertension [2, 5, 8-10, 14, 16-18], arteriosclerosis [3, 4, 15], HDL-cholesterol [4, 7, 8] and fibrinogen [7, 10] levels. In some case-control studies, it has also been shown a possible association between AAA and triglycerides [10, 20], cytokines [21-26], IL-6 [22-25], TNF-α [24-26], acute phase reactants [27, 28], oxidative stress [29], homocysteine [30, 31], cystatein-C [32], plasmin-antiplasmin complexes [33, 34], elastin peptides and its inhibition [35, 36], MMP-2 [37, 38], endothelin-1 [39], macrophage migration [40], PAF [41], connective tissue defects [42-46], and shear stress [47].

This study is based on the Malmö Preventive Study. Since we only noted six AAAs in women in the follow-up until now, we focused our analysis on the male population. Most studies do have selection bias. The majority included in this health screening analysis were men and the acceptable attendance rate was 71 per cent. Undetected small aneurysms at the health screening or during the follow-up cannot be ruled out, not even large asymptomatic aneurysms, because no diagnostic measures were made to assure whether there was any presence of aneurysms or not. These factors need to be taken into account when analysing our data. Furthermore, some individuals in the screened population have moved to other areas, which also should influence our results. However, we consider that the fairly large cohort of screened patients, followed for a median of over 20 years, still makes our results valuable, and the majority of clinical important aneurysms should have been recognized in our population.

Genetic studies have shown alterations in several genes exhibiting a pattern of chronic inflammation, matrix degradation, arteriosclerosis and smooth muscle cell depletion [48-53], but this knowledge is currently based on a limited screening of less then 1 per cent of the genome. A familial history regarding AAA among relatives was not taken at the health screening in our population cohorts. An association between familial incidence and AAA has been strongly documented [54, 55] and when based on our data from patient records, it supports a familial history. However, since it was not initially analysed in our health screening cohorts and known for the entire male group it is not possible to properly evaluate.

Another limitation with this, as for most other studies as well, is the suboptimal autopsy rates. In Malmö, a high autopsy rate remained until 1990 [56], and was acceptable until 2000, but it is currently as low as in most western countries with an autopsy rate of 10-15 per cent. In spite of this, we decided to include only objectively documented AAAs and we controlled the records on each patient who was included.

How predictive are the associated factors - male gender, smoking, physical inactivity and hypercholesterolemia - that we found? The likelihood for a factor or laboratory value 21 years before an AAA that was diagnosed in absolute risk was not high. The presence of male gender, smoking or high cholesterol value increased the risk of the development of AAA many times, but the majority of male, smoking, inactive patients with hypercholesterolemia, will not develop AAA. Nevertheless, our data are interesting and from an etiopathologic point of view we should focus our interest on these factors. In the future, maybe pharmacological treatment can prevent aneurysm formation?

Genetical studies have localised some of the probably many factors contributing to the development of aneurysm [48-53]. Even studies using beta-blockers, statins, anti-inflammatory drugs, or matrix proteinase-inhibition have found some effects on aneurysm growth.[57-59]

The screening for AAA is currently under debate. Maybe we have identified a group of subjects in whom screening should be most beneficial: inactive, smoking men with hypercholesterolemia. In the group having these factors, the absolute risk of developing AAA was five to10 times higher than in active, non-smoking, normocholesterolemic male patients. We know that screening programmes for AAA are cost-effective, but the mortality from AAA is only moderately reduced. [60,61]

In conclusion, we have found some factors associated with the development of AAA - male gender, smoking and hypercholesterolemia – in agreement with other studies and these have thus been further established. The fact that physically inactive patients were more prone to develop AAA is not an established associated factor. It is an interesting finding, but only based on a questionnaire 21 years before AAA was diagnosed and therefore it needs to be further studied. So far, 126 documented AAAs have been seen in males with 21 years of follow-up after the initial health screening. A later analysis of this material may be even more interesting, since the majority of aneurysms to occur in this cohort of 33 000 screened individuals have not jet been developed or diagnosed.

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Table I

Baseline characteristics at the time of the health screening programme of male individuals with detected AAA compared with a case control series (age-adjusted). Results (but no statistical comparison) on the total screened male population are also shown. Values presented as mean±SD.

	AAA-group (n=126)	Case-control group (n=126)	Screened males (n=22 244)
Age (years)	47±6.1	47±6.1	43.7±6.6
Length (cm)	178±7	176±8	177±7
BMI (kg/m^2)	25.4±3.2	24.9±3.3	24.7±3.3
Systolic BP (mmHg)	134±19	131±11	127±15
Diastolic BP (mmHg)	90±11**	86±11	85±10
COHb (%)	4.0±3.0	3.1±2.8	2.3±2.8
FVC (l/min)	4.2±0.9	4.2±0.8	4.5±0.9
FEV1.0 (l/s)	3.3±0.7	3.2±0.7	3.5±0.8
Smoking (%)	81 ***	51	51
Physical active (%)	20 ***	58	48

*=p<0.05, **=p<0.01,***=p<0.001 for comparison between AAA-group and case controls. BMI = body mass index, BP = blood pressure, COHb = carbon monoxide, FVC = forced vital capacity, FEV1.0 = forced expiratory volume in 1 sec.

Table II

Laboratory data at the time of the health screening programme of male individuals with detected AAA compared with a case control series (age-adjusted). Results, but without statistical comparison for the screened male population, also shown. Values presented as mean±SD.

	AAA-group (n=126)	Case-control group (n=126)	Screened males (n=22 244)
ESR (mm/h)	7.1±5.9	6.4±5.7	5.8±6.0
WBC (x10^9/L)	6.3±2.0	6.2±1.9	6.1±2.1
Hb (g/L)	146±9.7	147±9.3	148±9.7
Creatinine (µmol/l)	94±16	92±12	93±19
S-uric acid (µmol/l)	336±65*	318±67	324±64
S-total cholesterol (mmol/l)	6.3±1.1***	5.8±1.0	5.6±1.1
S-triglycerides (mmol/l)	1.9±1.2***	1.5±0.7	1.5±1.1
F-b-glucose (mmol/l)	4.9±0.8	4.8±0.7	5.0±1.0
S-GT (µkat/l)	0.73±0.50	0.90±1.48	0.69±0.96

*=p<0.05,**=p<0.01,***=p<0.001. S = serum, P = plasma, F = fasting, b = blood, ESR = erythrocyte sedimentation rate, WBC = white blood cell count, Hb = haemoglobin, GT = glutamic acid transferase.

Table III

Inflammatory-related proteins in 6 477 men (previously reported [10]) of whom 63 later (median 19 years) developed AAA.

	AAA-patients (n=63)	Male screening group (n=6 414)	
Fibrinogen (g/L)	3.95±0.65	3.50±0.80	p<0.001
Alfa1-antitrypsin (g/L)	1.40±0.28	1.27±0.27	p<0.001
Ceruloplasmin (g/L)	0.36±0.07	0.32±0.07	p<0.001
Orosmucoid (g/L)	0.91±0.23	0.82±0.20	p<0.001
Haptoglobin (g/L)	1.69±0.79	1.38±0.68	p<0.001

Table IV

Logistic regression analysis of variables found to significantly differ between the AAA group and the case control group (Odds ratio for 1 SD or yes/no questions, 95 % confidence intervals).

	Odds ratio	95 % conf.int.	p=
S-triglycerides	1.28	0.92-1.79	0.1453
Diastolic blood pressure	1.29	0.99-1.67	0.0692
S-cholesterol	1.45	1.05-1.99	0.0227
Physical inactivity	2.67	1.42-5.01	0.0022
Smoking	3.51	1.92-6.44	<0.0001

Figure I

The absolute risk of the development of AAA depending on the level of cholesterol (divided in four quartiles, with small differences due to the fact that many had equal values).

	% absolute risk	No. of AAA	No. at risk
Cholesterol quartile			
1. (Lowest)	0.1 %	7	5 585
2.	0.4 %	21	5 582
3.	0.6 %	34	5 696
4. (Highest)	1.2 %	64	5 540

Figure(s)

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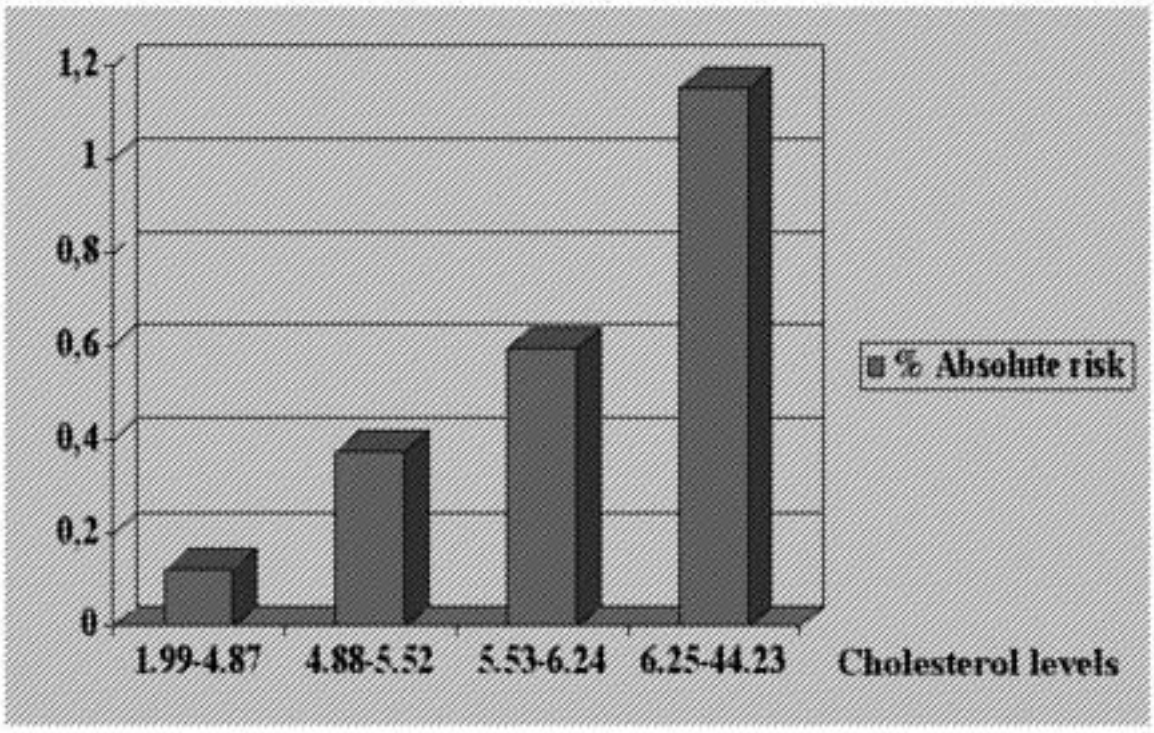

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* e.g. Study design, Data collection, Data analysis, or Writing

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Factors associated with development of large abdominal aortic aneurysm in middle-aged men.

Short title: Associated factors for development of AAA

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Abstract

Objectives: To investigate whether any variables in a health-screened population study were associated with later development of large abdominal aortic aneurysms (AAA).

Setting: Malmö, southern Sweden.

Material and methods: Within the Malmö Preventive Study 22 444 men and 10 982 women were investigated between 1974 and 1991. The mean age at the health screening was 43.7 years.

Results: After a median follow-up of 21 years, 126 men and six women ($p<0.001$) had large AAA that were symptomatic or evaluated for operation (5 cm diameter or more) or had autopsy-verified ruptured AAA. The male group (mean age 47 years) was, because of difference in age ($p<0.001$) also compared with an age-matched control group. The male patients with AAA showed increased diastolic blood pressure ($p<0.007$) at the health screening. Smoking predicted the development of AAA ($p<0.0001$). No difference in forced vital capacity or BMI was seen. Those who were physically inactive (e.g. not walking or cycling to work) had an increased risk of developing AAA ($p<0.001$). Among the laboratory markers measured, the erythrocyte sedimentation rate did not differ (7.1±5.9 vs. 6.4±5.7), but cholesterol (6.3±1.12 vs. 5.8±1.0) ($p<0.0001$) and triglycerides (1.9±0.12 vs. 1.5±0.07) ($p<0.001$) were significantly elevated in these individuals who subsequently developing AAA. The inflammatory proteins alfa-1-antitrypsin, ceruloplasmin, orosmucoid, fibrinogen, and haptoglobulin were increased ($p<0.001$).

Conclusion: Male gender, smoking, physical inactivity and cholesterol are significant factors associated with the development of AAA.

Key words: AAA, associated risk factors, atherosclerosis, smoking, hypercholesterolemia, inflammatory markers.

Introduction

Abdominal aortic aneurysm (AAA) is relatively common in elderly men. Elastin and collagen degradation, increased activity of matrix metalloproteinases, inflammatory and immunologic activity, as well as altered wall shear stress, may be causative factors for the development of AAA [1]. There are few studies on factors associated with the development of AAA during long-time follow-up in apparently healthy individuals [2-3]. Most studies have analysed subpopulations or patients with confirmed AAA [4-10]. Previous studies have shown age, male gender, smoking, hypertension and high cholesterol levels to be associated with the development of AAA [2-10].

The evaluation of the incidence of AAA was previously based on autopsy findings, selected case studies, but also on population screening studies in which ultrasonography was used. In this study no initial screening for AAA was made and we included only those from our population cohort who had symptomatic AAA or AAA with a diameter larger than 5 cm and were evaluated for treatment or autopsy-proven ruptured AAA. The aim of this study was to determine the risk factors associated with development of large AAA in a population-based cohort.

Material and Methods

The Malmö Prevention Project[11,12] is a health screening and intervention programme carried out during a 17-year period (1974-1991). A total of 22 444 men (mean age 43.7±7 years) participated (participation rate 71%), of whom 126 were found to develop AAA. The health screening programme also included a population of 10 982 women, but in this group only six individuals have been diagnosed with the development of AAA ($p<0.001$).

Health Screening Procedure

The health screening and examination procedures have previously been described in detail.[11, 12] In brief; heart rate and blood pressure (BP) were measured in the right arm after 10 minutes' rest. Body mass index (BMI) was calculated as kg/m^2. Diabetes mellitus was considered to be present, if there was a history of treatment of diabetes or a fasting blood glucose level of more than 6.7 mmol/l or equal. Smoking was defined as current smoking at the time of participation in the health screening programme. Forced vital lung capacity (FVC), measured with a Spiroton apparatus (Drägerwerk AG, Lübeck, Germany), and activity assessed from a questionnaire decided the measure of physical fitness. The use of blood pressure-lowering drugs, heart glycosides, nitro vasodilators and analgesic drugs was recorded.

Venous blood was collected after an overnight fast in order to determine the erythrocyte sedimentation rate (ESR), hematocrit and haemoglobin (Hb) levels, total leukocyte count, platelet count, and serum total cholesterol, triglycerides, total calcium, albumin, creatinine, electrolytes, gamma glutamic acid transferase (GT), alanine amino transferase (ALAT), aspartate amino transferase (ASAT), alkaline phosphatases (ALP) and uric acid. The analyses were performed by routine methods at the Clinical Chemistry Laboratory of Malmö University Hospital. The fasting capillary blood glucose level was determined in all subjects.

Individuals who were health-screened and had hypertension, hyperlipidemia, diabetes mellitus or pathological glucose tolerance or high alcohol intake were offered

intervention and referred to outpatient clinics. The Ethics Committee at Lund University approved the study. All participants gave informed consent.

Patients and control groups

During the 28 years between the start of this health screening programme and December 31, 2002, 126 men and six women of this cohort were documented to have symptomatic or large (5-5.5 cm in diameter) AAA. They either underwent operative reconstruction (n=98), were evaluated for aneurysm exclusion, but treated conservatively (n=19), or were found to have autopsy-verified ruptured AAA (n=15). This documentation was based on hospital register data, SwedVasc quality control data and death certificates. Only those who had objectively documented treatment-requiring AAA were included in the analysed group.

Plasma protein analyses were performed in a subgroup of 6 477 men of whom 63 developed AAA. Details have been separately reported [10], but are included to give as much information as possible on the factors associated with the development of AAA.

Male patient baseline values for the different variables at the time of health screening were compared with the corresponding values for the case control group established because of differences in age. The closest birth date case not having AAA was selected to the control group, but also to the entire screened male population cohort (n=22 444 [6 477 regarding plasma protein analyses]).

Statistics

Values are presented as mean ± SD. The differences between groups were assessed with the Mann-Whitney U test, or the Chi-squared test as appropriate. Because of the multiple comparisons, a post-hoc adjustment using Bonferroni's correction of p values was performed, revealing that only p values below 0.01 should be considered as truly significant. The relative risk of the development of AAA was estimated in terms of the odds ratio (OR) and the 95-per cent confidence interval (CI) for a one standard deviation increase (for measurable variables) or in terms of the presence versus absence of a given factor as determined by a logistic regression analysis. The independent significance of each variable was assessed by a multiple logistic regression analysis after adjustment for other significant risk factors. In this analysis p values less than 0.05 were considered statistically significant.

Results

Six women and 126 men developed AAA during the observation period ($p<0.0001$). The median time between the health screening and detection of AAA was 21 years (range 6-30 years), and the median age at the detection of AAA was 68 years (range 49-81 years). Male patients with AAA (n=126) were further analysed. At the health screening, this group was significantly older (47[37-60] years) than the entire screened male population (n=22 444, 43.7[26-61] years; $p<0.0001$). Therefore, we established an age-adjusted case control group with 126 patients. Demographic data at health screening are seen in Table I. The male patients with AAA had higher diastolic blood pressure (134/90 mmHg versus 131/86 mmHg; $p<0.007$).

A significantly higher proportion of the patients with AAA were smokers at the health screening (81% versus 51%; $p<0.0001$). Those who had smoked daily for more than 10 years were even more frequent among the patients who developed AAA ($p<0.0001$). The subgroup of pipe smokers also seemed to have an increased risk ($p<0.08$).

Reported alcohol consumption was not a risk factor for the development of AAA. Neither were factors such as being busy, easily stressed or suffering from insomnia associated with later development of AAA. The initial questionnaire from the health screening showed that the case control group and entire male population were more physical active ($p<0.001$) than those who developed AAA. Forced vital capacity did, however, not differ.

Laboratory data (Table II) showed increased serum total cholesterol (6.3±1.1 mmol/l versus 5.9±1.0 mmol/l; $p<0.0001$), triglyceride (1.9±1.2 mmol/l versus 1.5±0.7 mmol/l; $p<0.0001$), and plasma fibrinogen levels (3.95±0.65 mmol/l versus 3.50±0.80 mmol/l; $p<0.001$, Table III) in subjects later developing AAA.

We did not find any differences regarding the recorded use of medication between the patients with AAA and the control group or the background health-screened population. Furthermore, a logistic regression analysis was performed to evaluate the variables that differed as factors associated with later AAA. Smoking, physical inactivity, and serum cholesterol remained as independent associated factors (Table IV). Since fibrinogen was only analysed in a subgroup of 63 patients with AAA and 6 477 of the background population, a separate logistic regression analysis was performed in this group in which fibrinogen was not an independent predictor ($p=0.062$).

There were no differences concerning the health screening variables between subjects operated on because of ruptured, symptomatic or asymptomatic AAA. Neither were there any significant differences concerning associated factors in the patients with AAA, with different time intervals between the health screening and the development of AAA below or above the median of 21 years after screening (data not shown).

The absolute risk of developing a large AAA during a 21-year follow-up of initially 47-year-old men was 0.56 per cent, which was increased among the smokers to 0.9 per cent (100 AAA among 11 403 smokers) compared with 0.2 per cent among the non-smokers (26 AAA among11 041 non-smokers). In Table V, we show the absolute risk of different quartiles of serum-total cholesterol. In the highest quartile, we saw an absolute risk of 1.2 per cent compared with 0.1 per cent in the lowest quartile of serum-total cholesterol values.

Discussion

In recent years, we have learned much about the pathology of AAA. Some of the more important factors are elastolysis, impaired collagen production and increased degradation, increased levels of matrix proteinases, inflammatory reactions with increased CRP levels, leukocyte and macrophage accumulation in the aneurysmal wall, and increased immunological activity [1].

This study verifies earlier population-based studies showing several factors associated with the development of AAA such as male gender, smoking and high cholesterol levels [2-10]. A large number of case control studies on patients with AAA have focused on these

risk factors, and an association has been further verified between AAA and age [4, 5, 7-9], male gender [4-10, 13-19], smoking [2-10, 13-17], total cholesterol [3, 5, 8-10] and suggested by several studies for hypertension [2, 5, 8-10, 14, 16-18], arteriosclerosis [3, 4, 15], HDL-cholesterol [4, 7, 8] and fibrinogen [7, 10] levels. In some case-control studies, an association has been demonstrated between AAA and triglycerides [10, 20], cytokines [21-26], IL-6 [22-25], TNF-α [24-26], acute phase reactants [27, 28], oxidative stress [29], homocysteine [30, 31], cystatein-C [32], plasmin-antiplasmin complexes [33, 34], elastin peptides and its inhibition [35, 36], MMP-2 [37, 38], endothelin-1 [39], macrophage migration [40], PAF [41], connective tissue defects [42-46], and shear stress [47].

This study is based on the Malmö Preventive Study. Since we only noted six AAAs in women in the follow-up until now, we focused our analysis on the male population. Most studies do have selection bias. The majority included in this health screening analysis were men and the acceptable attendance rate was 71 per cent. Undetected aneurysms at the health screening or during the follow-up cannot be ruled out, because patients were not routinely imaged. These factors need to be taken into account when analysing our data. Furthermore, some individuals in the screened population have moved to other areas, which also may have influenced our results. Another limitation with our study is the suboptimal autopsy rates. In Malmö, a high autopsy rate remained until 1990 [56], and was acceptable until 2000, but it is currently as low as in most western countries with an autopsy rate of 10-15 per cent. However, we consider that the fairly large cohort of screened patients, followed for a median of over 20 years, still makes our results valuable, and the majority of clinically important aneurysms should have been recognized in our population.

Genetic studies have shown alterations in several genes exhibiting a pattern of chronic inflammation, matrix degradation, arteriosclerosis and smooth muscle cell depletion [48-53], but this knowledge is currently based on a limited screening of less then 1 per cent of the genome. A familial history regarding AAA among relatives was not taken at the health screening in our population cohorts. An association between familial incidence and AAA has been strongly documented [54, 55].

How predictive are the associated factors - male gender, smoking, physical inactivity and hypercholesterolemia - that we found? The presence of male gender, smoking or high cholesterol value increased the risk of the development of AAA many times, but the majority of male, smoking, inactive patients with hypercholesterolemia, will not develop AAA. In the future, maybe pharmacological treatment can prevent aneurysm formation? Genetical studies have localised some of the factors contributing to the development of aneurysm [48-53]. Studies using beta-blockers, statins, anti-inflammatory drugs, or matrix proteinase-inhibition have found some effects on aneurysm growth.[57-59]

Screening for AAA is currently under debate. Inactive, smoking men with hypercholesterolemia are a sub-group likely to benefit from screening. In the group having these factors, the absolute risk of developing AAA was five to10 times higher than in active, non-smoking, normocholesterolemic male patients. We know that screening programmes for AAA are cost-effective, but the mortality from AAA is only moderately reduced. [60,61]

In conclusion, we have confirmed male gender, smoking and hypercholesterolemia to be associated with the development of AAA. The fact that physically inactive patients

were more prone to develop AAA was not previously established. It is an interesting finding, but only based on a questionnaire 21 years before AAA was diagnosed and therefore it needs to be further confirmed. So far, 126 documented AAAs have been seen in males with 21 years of follow-up after the initial health screening.

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Table I

Baseline characteristics at the time of the health screening programme of male individuals with detected AAA compared with a case control series (age-adjusted). Results (but no statistical comparison) on the total screened male population are also shown. Values presented as mean±SD.

	AAA-group (n=126)	Case-control group (n=126)	Screened males (n=22 244)
Age (years)	47±6.1	47±6.1	43.7±6.6
Length (cm)	178±7	176±8	177±7
BMI (kg/m^2)	25.4±3.2	24.9±3.3	24.7±3.3
Systolic BP (mmHg)	134±19	131±11	127±15
Diastolic BP (mmHg)	90±11**	86±11	85±10
COHb (%)	4.0±3.0	3.1±2.8	2.3±2.8
FVC (l/min)	4.2±0.9	4.2±0.8	4.5±0.9
FEV1.0 (l/s)	3.3±0.7	3.2±0.7	3.5±0.8
Smoking (%)	81 ***	51	51
Physical active (%)	20 ***	58	48

*=p<0.05, **=p<0.01,***=p<0.001 for comparison between AAA-group and case controls. BMI = body mass index, BP = blood pressure, COHb = carbon monoxide, FVC = forced vital capacity, FEV1.0 = forced expiratory volume in 1 sec.

Table II

Laboratory data at the time of the health screening programme of male individuals with detected AAA compared with a case control series (age-adjusted). Results, but without statistical comparison for the screened male population, also shown. Values presented as mean±SD.

	AAA-group (n=126)	Case-control group (n=126)	Screened males (n=22 244)
ESR (mm/h)	7.1±5.9	6.4±5.7	5.8±6.0
WBC (x10^9/L)	6.3±2.0	6.2±1.9	6.1±2.1
Hb (g/L)	146±9.7	147±9.3	148±9.7
Creatinine (µmol/l)	94±16	92±12	93±19
S-uric acid (µmol/l)	336±65*	318±67	324±64
S-total cholesterol (mmol/l)	6.3±1.1***	5.8±1.0	5.6±1.1
S-triglycerides (mmol/l)	1.9±1.2***	1.5±0.7	1.5±1.1
F-b-glucose (mmol/l)	4.9±0.8	4.8±0.7	5.0±1.0
S-GT (µkat/l)	0.73±0.50	0.90±1.48	0.69±0.96

*=$p<0.05$,**=$p<0.01$,***=$p<0.001$. S = serum, P = plasma, F = fasting, b = blood, ESR = erythrocyte sedimentation rate, WBC = white blood cell count, Hb = haemoglobin, GT = glutamic acid transferase.

Table III

Inflammatory-related proteins in 6 477 men (previously reported [10]) of whom 63 later (median 19 years) developed AAA.

	AAA-patients (n=63)	Male screening group (n=6 414)	
Fibrinogen (g/L)	3.95±0.65	3.50±0.80	p<0.001
Alfa1-antitrypsin (g/L)	1.40±0.28	1.27±0.27	p<0.001
Ceruloplasmin (g/L)	0.36±0.07	0.32±0.07	p<0.001
Orosmucoid (g/L)	0.91±0.23	0.82±0.20	p<0.001
Haptoglobin (g/L)	1.69±0.79	1.38±0.68	p<0.001

Table IV

Logistic regression analysis of variables found to significantly differ between the AAA group and the case control group (Odds ratio for 1 SD or yes/no questions, 95 % confidence intervals).

	Odds ratio	95 % conf.int.	p=
S-triglycerides	1.28	0.92-1.79	0.1453
Diastolic blood pressure	1.29	0.99-1.67	0.0692
S-cholesterol	1.45	1.05-1.99	0.0227
Physical inactivity	2.67	1.42-5.01	0.0022
Smoking	3.51	1.92-6.44	<0.0001

Figure I

The absolute risk of the development of AAA depending on the level of cholesterol (divided in four quartiles, with small differences due to the fact that many had equal values).

	% absolute risk	No. of AAA	No. at risk
Cholesterol quartile			
1. (Lowest)	0.1 %	7	5 585
2.	0.4 %	21	5 582
3.	0.6 %	34	5 696
4. (Highest)	1.2 %	64	5 540