ORIGINAL INVESTIGATION

The Aneurysm Detection and Management Study Screening Program

Validation Cohort and Final Results

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Background: We previously reported the prevalence and associations of abdominal aortic aneurysm (AAA) in 73 451 veterans aged 50 to 79 years who underwent ultrasound screening.

Objective: To understand the prevalence of and principal positive and negative risk factors for AAA, and to assess reproducibility of our previous findings.

Methods: In the new cohort of veterans undergoing screening, 52 745 subjects aged 50 to 79 without history of AAA underwent successful ultrasound screening for AAA, after completing a questionnaire on demographics and potential risk factors.

Results: We detected AAA of 4.0 cm or larger in 613 participants (1.2%; compared with 1.4% in the earlier cohort). The direction and magnitude of the important associations reported in the first cohort were confirmed. Respective odds ratios for the major associations with AAA for the second and for the combined cohorts were as follows: 1.81 and 1.71 for age (per 7 years), 0.12 and 0.18 for female sex, 0.59 and 0.53 for black race, 1.94 and 1.94 for family history of AAA, 4.45 and 5.07 for smoking, 0.50 and 0.52 for diabetes, and 1.60 and 1.66 for atherosclerotic diseases. The excess prevalence associated with smoking accounted for 75% of all AAAs of 4.0 cm or larger in the total population of 126 196. Associations for AAA of 3.0 to 3.9 cm were similar but tended to be somewhat weaker.

Conclusions: Our findings confirm our previous cohort findings. Age, smoking, family history of AAA, and atherosclerotic diseases remained the principal positive associations with AAA, and female sex, diabetes, and black race remained the principal negative associations.

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AORTIC ANEURYSM is the tenth leading cause of death in older men.[1] Most of these deaths are caused by rupture or elective repair of abdominal aortic aneurysm (AAA). Strategies to reduce AAA mortality are needed and will require a clear understanding of the etiology and epidemiological features of the disease. In a previous article, we reported the prevalence and associations of AAA in 73 451 veterans aged 50 to 79 years who underwent ultrasound screening.[2] Some of the principal findings of that study (eg, that the excess prevalence associated with smoking accounted for three fourths of all AAAs with diameter ≥4.0 cm, and that diabetes was associated with a substantially reduced prevalence of AAA) were unexpected and required confirmation. The purpose of our present article is to report the final results of the Aneurysm Detection and Management (ADAM) study screening program of the Department of Veterans Affairs (VA) and to attempt to validate our previous results by comparing them with those obtained from subjects undergoing screening after the first cohort.

RESULTS

In the second cohort, 52 943 subjects aged 50 to 79 years without history of AAA underwent screening, 198 of whom were excluded because the aorta could not be visualized. The remaining 52 745 subjects constitute the study group. As shown in **Table 1**, the second cohort consisted largely of men with a history of smoking and closely resembled the first cohort in most respects, although atherosclerotic diseases were somewhat less common.

Abdominal aortic aneurysm, defined as infrarenal aortic diameter of 3.0 cm or larger, was detected in 1917 subjects (3.6%), and in 613 (1.2%), AAA were 4.0 cm or larger. The frequencies of AAA

SUBJECTS AND METHODS

The ADAM study is an ongoing randomized clinical trial comparing immediate surgery with imaging surveillance in patients aged 50 to 79 years with asymptomatic AAA of 4.0 to 5.4 cm in diameter.[3] To support recruitment into the trial, ultrasound screening clinics were established at participating VA medical centers. Subjects undergoing screening before April 1995 were described in the first cohort, and those undergoing screening from April 1, 1995, to the end of the screening program on July 31, 1997, are included in the second (new) cohort. In June 1995, screening ended at one of the original 15 centers and began at a new 16th center. The study was approved by the human rights committee at the VA Cooperative Studies Program coordinating center and by the institutional review boards at the 16 participating centers.

Details of the design of the screening program have been reported previously[2] and are reviewed briefly herein. The first cohort consisted almost entirely of active patients at the participating centers (those treated in the current or previous fiscal year or having future appointments) who responded to an initial invitation letter. The second cohort consisted of active VA patients who responded to repeated mailings and to various advertising and outreach strategies used by the screening clinics. Those aged 50 to 79 years are included in the analysis. Inadvertent second screenings were identified by social security numbers, and the later screening was excluded. As in our previous article,[2] subjects who reported having been told in the past that they had AAA were also excluded.

Before undergoing the ultrasound examination, all subjects completed a brief questionnaire that addressed demographic information and possible risk factors for AAA. The abdominal aorta was measured above and below the renal arteries using a 3.5-mHz real-time sector scanner. Abdominal aortic aneurysm was defined by infrarenal aortic diameter by the use of the maximum external diameter in any direction at the widest point of any dilation and cutoff points of 3.0 and 4.0 cm. A cutoff point of 3.0 cm is often used to define AAA, but many subjects with infrarenal aortic diameters of 3.0 through 3.9 cm would not be considered to have true AAA by some authors. Because diameters of 3.0 to 3.9 cm are more numerous than those of 4.0 cm or larger and may not all represent true disease, including them in the regression models could obscure or dilute the effect of the true AAAs. Therefore, as in the earlier article, we report separate regression models for AAA of 3.0 to 3.9 cm and of 4.0 cm or larger, each compared with subjects having infrarenal aortic diameters of less than 3.0 cm.

Analyses to determine the associations between the items on the questionnaire and the presence of AAA in the second cohort were performed by means of univariable and multivariable logistic regression as described for the first cohort.[2] We also examined AAA prevalence and associations when both cohorts were combined. We included second cohort (vs first) as a factor in the combined cohort regression models to assess the adjusted difference in AAA prevalence between cohorts, and also examined interactions between this variable and each of the other variables. A significant interaction between a variable and the second cohort variable served to indicate that the difference from cohort to cohort in the association of that variable with AAA was statistically significant.

by diameter are shown in **Table 2**. The prevalence of AAA was lower in the second cohort, with an unadjusted odds ratio (OR) of 0.79 (95% confidence interval [CI], 0.74-0.83) for AAA of 3.0 cm or larger in the second vs first cohort.

The results of the multivariable analyses are shown in **Table 3** and **Table 4**. In each cohort and in the combined group, correlations between factors were less than 0.50 except for values of 0.78 to 0.79 between weight and waist circumference. The prevalence of AAA remained significantly lower in the second cohort than in the first in the multivariable models, as indicated by the CIs of the ORs for second vs first cohort . Nevertheless, the ORs for the various factors were similar in both cohorts. All significant associations identified in the first cohort remained significant in the second except for hypertension and chronic obstructive pulmonary disease in Table 4, and these associations were again significant in the analysis of the combined group. In addition, 2 previously insignificant associations (cerebral vascular disease and cancer in Table 4) were significant in the second cohort and remained significant for the combined group. Significant interaction with the second vs the first cohort variable (indicating a significantly different association with AAA between cohorts for that variable) was seen for several variables in each model, as indicated in Tables 3 and 4, but the differences were small and of questionable clinical importance.

The direction and magnitude of the important associations reported in the first cohort were thus confirmed in the second cohort. Age, smoking, family history of AAA, and atherosclerotic diseases remained the principal positive associations with AAA, and female sex, diabetes, and black race remained the principal negative associations. The association of AAA with smoking was stronger for AAA of 3.0 to 3.9 cm and weaker for AAA of 4.0 cm or larger in the second cohort compared with the first, but neither change was statistically significant, and smoking remained the strongest association, along with age and sex. The unexpected strong negative association of AAA with diabetes observed in the first cohort was slightly (though not significantly) stronger for both AAA diameter models in the second cohort.

The excess prevalence associated with smoking (the etiologic fraction[4]) accounted for 72% of all AAAs of 4.0 cm or larger in the second cohort, compared with 78% in the first cohort and 75% in the combined group, again suggesting that smoking may be responsible for most clinically important, previously undiagnosed AAA.

The data from the second cohort also confirmed that the association of smoking with AAA increases significantly with the number of years smoked (OR [95% CI]

Table 1. Characteristics of Veterans Undergoing Screening for Abdominal Aortic Aneurysm*

Characteristic	First Cohort (n = 73 451)	Second Cohort (n = 52 745)	Combined Group (n = 126 196)
Age, mean ± SD, y	66.2 ± 7.1	65.6 ± 8.0	66.0 ± 7.5
Male sex	97.2	97.4	97.3
Race†			
White	87.0	86.1	86.6
Black	8.2	8.2	8.2
Other	4.9	5.7	5.2
Height, mean ± SD, cm	176.4 ± 7.3	176.7 ± 7.3	176.5 ± 7.3
Weight, mean ± SD, kg	84.8 ± 15.7	85.6 ± 16.0	85.1 ± 15.8
Waist circumference, mean ± SD, cm	96.4 ± 11.3	96.1 ± 11.2	96.2 ± 11.3
Family history of AAA	5.1	5.0	5.0
Ever smoked regularly‡	75.5	73.9	74.8
No. of years smoked, mean ± SD	30.1 ± 14.6	28.6 ± 14.5	29.4 ± 14.6
Current smoker	18.7	18.1	18.4
Hypertension	55.1	52.6	54.1
High cholesterol level	52.3	52.4	52.3
Coronary artery disease	39.0	33.6	36.8
Claudication	6.7	5.0	6.0
Cerebral vascular disease	11.5	9.8	10.8
Any atherosclerosis	46.0	39.8	43.4
Deep venous thrombosis	7.4	6.4	7.0
Diabetes mellitus	18.1	17.1	17.7
Chronic obstructive pulmonary disease	14.4	12.1	13.4
Nonskin cancer	12.4	12.0	12.3
Abdominal imaging in past 5 y	19.5	16.7	18.3

*Unless otherwise indicated, data are given as percentage of subjects. AAA indicates abdominal aortic aneurysm. P<.05 for all comparisons between first and second cohort except family history of AAA.

†Percentages have been rounded and may not sum 100.

‡Indicates more than 100 cigarettes during lifetime.

per 10 years, 1.17 [1.10-1.25] for 3.0-3.9 cm and 1.13 [1.04-1.24] for ≥4.0 cm, compared with 1.18 [1.13-1.24] and 1.09 [1.02-1.16], respectively, in the first cohort) and decreases significantly with number of years after quitting smoking (OR [95% CI] per 10 years, 0.78 [0.72-0.84] for 3.0-3.9 cm and 0.73 [0.66-0.82] for ≥4.0 cm, compared with 0.81 [0.76-0.86] and 0.72 [0.65-0.79], respectively, in the first cohort) when these variables were added to the models. After adjustment for number of years smoked (and all other variables), current smokers were again more likely than ex-smokers to have AAA (OR [95% CI], 1.51 [1.19-1.90] for AAA ≥4.0 cm compared with 1.63 [1.37-1.94] in the first cohort).

Table 2. Prevalence of Abdominal Aortic Aneurysm by Diameter*

Diameter, cm	First Cohort (n = 73 451)	Second Cohort (n = 52 745)	Combined Group (n = 126 196)
≥3.0	3366 (4.6)	1917 (3.6)	5283 (4.2)
≥4.0	1031 (1.4)	613 (1.2)	1644 (1.3)
≥5.0	368 (0.50)	203 (0.38)	571 (0.45)
≥5.5†	224 (0.30)	118 (0.22)	342 (0.27)
≥6.0	137 (0.19)	75 (0.14)	212 (0.17)
≥7.0	48 (0.07)	28 (0.05)	76 (0.06)
≥8.0	22 (0.03)	10 (0.02)	32 (0.03)

*Data are given as number (percentage) of subjects.

†The diameter at which surgery was offered in the surveillance arms of the Aneurysm Detection and Management trial and the United Kingdom Small Aneurysm Trial.[3]

COMMENT

In this article, we have confirmed the important findings from our earlier screening cohort in a second validation cohort and have combined both cohorts to report the prevalence and associations of AAA in a large population. Our cohorts were drawn from the same population and were very similar, as shown in Table 1. Our study thus addresses the reproducibility, and not the transportability, of our previous results,[5] and we advise caution in generalizing our findings to other populations.

Despite the similarity between the two cohorts, the prevalence of AAA was somewhat lower in the second cohort than in the first. The reason for this difference is not clear, but it presumably results from a time trend (eg, more AAA diagnosed before screening over time) or from the small differences in the ways the two cohorts were assembled. Despite the difference in AAA prevalence between cohorts, the direction and magnitude of the associations with AAA were very similar. Age, male sex, and smoking history remained the strongest associations, followed by family history of AAA and the negative association with diabetes. Other important associations included atherosclerotic diseases and the negative association with black race.

Because of the statistically significant differences in characteristics between cohorts (Table 1) and the difference in AAA prevalence, our decision to combine the cohorts could be questioned. We combined the results because the differences in characteristics were generally small and because the screening program was designed and

Table 3. Multivariable Models of Associated Factors for Abdominal Aortic Aneurysm of 3.0 to 3.9 cm in Diameter vs Normal Infrarenal Aortic Diameter*

Factors	Odds Ratios (95% Confidence Intervals)		
	First Cohort (2217/66 638)†	Second Cohort (1237/47 781)†	Combined Group (3455/114 567)†
Age (per 7 y‡)	1.52 (1.45-1.60)	1.67 (1.57-1.78)	1.58 (1.52-1.64)
Female sex	0.62 (0.41-0.94)	0.20 (0.07-0.54)	0.47 (0.32-0.69)
Black race (vs white)	0.72 (0.59-0.87)	0.44 (0.32-0.61)§	0.62 (0.53-0.73)
Other race (vs white)	0.85 (0.67-1.09)	0.82 (0.59-1.14)	0.83 (0.68-1.01)
Height (per 7 cm‡)	1.20 (1.14-1.26)	1.20 (1.12-1.28)	1.19 (1.15-1.24)
Weight (per 16 kg‡)	0.97 (0.89-1.06)	1.04 (0.93-1.17)	1.00 (0.93-1.07)
Waist circumference (per 11 cm‡)	1.06 (0.98-1.14)	1.02 (0.92-1.13)	1.04 (0.98-1.11)
Family history of AAA	1.96 (1.68-2.28)	1.92 (1.57-2.35)	1.93 (1.71-2.18)
Ever smoked regularly‖	2.72 (2.37-3.11)	3.49 (2.87-4.24)	2.97 (2.65-3.32)
Hypertension	1.25 (1.14-1.37)	1.20 (1.06-1.35)	1.23 (1.14-1.32)
High cholesterol level	1.33 (1.20-1.48)	1.53 (1.33-1.76)	1.40 (1.29-1.52)
Coronary artery disease	1.42 (1.30-1.55)	1.46 (1.30-1.65)	1.44 (1.34-1.55)
Claudication	1.39 (1.20-1.62)	1.26 (1.00-1.59)	1.35 (1.18-1.53)
Cerebral vascular disease	1.22 (1.09-1.37)	1.41 (1.19-1.65)§	1.28 (1.17-1.41)
Any atherosclerosis¶	1.57 (1.44-1.72)	1.70 (1.50-1.91)	1.64 (1.52-1.78)
Deep venous thrombosis	0.90 (0.76-1.06)	1.04 (0.83-1.30)	0.95 (0.83-1.08)
Diabetes mellitus	0.68 (0.60-0.77)	0.60 (0.50-0.71)	0.65 (0.59-0.72)
Chronic obstructive pulmonary disease	1.04 (0.92-1.16)	1.11 (0.95-1.30)	1.06 (0.97-1.17)
Nonskin cancer	0.90 (0.80-1.03)	0.89 (0.75-1.06)	0.90 (0.81-1.00)
Abdominal imaging in past 5 y	1.06 (0.96-1.18)	0.86 (0.73-1.01)§	1.00 (0.91-1.09)
Second cohort (vs first)	. . .	. . .	0.81 (0.76-0.88)

*Normal infrarenal aortic diameter is defined as less than 3.0 cm. AAA indicates abdominal aortic aneurysm; ellipses, not applicable.
†Numbers in parentheses represent number of cases/controls.
‡Approximately 1 SD.
§The association differed significantly between both cohorts ($P<.05$ for interaction with second-cohort term).
‖More than 100 cigarettes during lifetime.
¶From a separate logistic model in which coronary artery disease, cerebral vascular disease, and claudication were combined into a single variable.

Table 4. Multivariable Models of Associated Factors for Abdominal Aortic Aneurysm of at Least 4.0 cm in Diameter vs Normal Infrarenal Aortic Diameter*

Factors	Odds Ratios (95% Confidence Intervals)		
	First Cohort (985/66 638)†	Second Cohort (583/47 781)†	Combined Group (1568/114 419)†
Age (per 7 y‡)	1.65 (1.53-1.78)	1.81 (1.65-1.99)	1.71 (1.61-1.82)
Female sex	0.22 (0.07-0.68)	0.12 (0.02-0.88)	0.18 (0.07-0.48)
Black race (vs white)	0.49 (0.35-0.69)	0.59 (0.39-0.91)	0.53 (0.40-0.69)
Other race (vs white)	0.91 (0.63-1.33)	1.19 (0.79-1.79)	1.02 (0.77-1.35)
Height (per 7 cm‡)	1.21 (1.12-1.30)	1.17 (1.06-1.28)	1.19 (1.12-1.26)
Weight (per 16 kg‡)	1.08 (0.95-1.23)	1.01 (0.86-1.19)	1.06 (0.96-1.17)
Waist circumference (per 11 cm‡)	1.15 (1.03-1.29)	1.19 (1.03-1.38)	1.16 (1.07-1.27)
Family history of AAA	1.95 (1.56-2.43)	1.94 (1.45-2.59)	1.94 (1.63-2.32)
Ever smoked regularly§	5.57 (4.24-7.31)	4.45 (3.27-6.05)	5.07 (4.13-6.21)
Hypertension	1.16 (1.01-1.32)	1.14 (0.96-1.36)	1.15 (1.03-1.28)
High cholesterol level	1.54 (1.31-1.80)	1.29 (1.06-1.58)	1.44 (1.27-1.63)
Coronary artery disease	1.62 (1.41-1.84)	1.36 (1.14-1.62)‖	1.52 (1.37-1.68)
Claudication	0.96 (0.74-1.25)	1.26 (0.88-1.80)	1.05 (0.85-1.30)
Cerebral vascular disease	1.19 (0.99-1.42)	1.45 (1.15-1.84)	1.28 (1.11-1.47)
Any atherosclerosis¶	1.68 (1.47-1.92)	1.60 (1.35-1.90)	1.66 (1.49-1.84)
Deep venous thrombosis	0.67 (0.50-0.88)	0.67 (0.46-0.99)	0.67 (0.53-0.84)
Diabetes mellitus	0.54 (0.44-0.65)	0.50 (0.39-0.65)	0.52 (0.45-0.61)
Chronic obstructive pulmonary disease	1.28 (1.09-1.50)	1.08 (0.86-1.36)	1.21 (1.06-1.38)
Nonskin cancer	0.90 (0.74-1.09)	0.64 (0.48-0.84)‖	0.80 (0.68-0.93)
Abdominal imaging in past 5 y	0.80 (0.67-0.94)	0.73 (0.57-0.93)	0.77 (0.67-0.89)
Second cohort (vs first)	. . .	. . .	0.86 (0.77-0.95)

*Normal infrarenal aortic diameter is defined as less than 3.0 cm. AAA indicates abdominal aortic aneurysm; ellipses, not applicable.
†Numbers in parentheses represent number of cases/controls.
‡Approximately 1 SD.
§More than 100 cigarettes during lifetime.
‖The association differed significantly between cohorts ($P<.05$ for interaction with second-cohort term).
¶From a separate logistic model in which coronary artery disease, cerebral vascular disease, and claudication were combined into a single variable.

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performed as a continuum, with the break point between cohorts chosen arbitrarily, although coinciding with the end of the first round of invitation letters at most centers. Our important findings do not depend on the cohorts being combined, however, and some readers may wish to disregard the combined results.

The excess prevalence associated with smoking accounted for approximately 75% of all AAA of 4.0 cm or greater in the combined group, again supporting the hypothesis that AAA is primarily a smoking-related disease. The mechanisms by which smoking could promote AAA formation remain unknown, but may involve decreased aortic elasticity, which has been linked to smoking[6] and to AAA.[7,8] Shapiro[9] has suggested that smoking may induce macrophages to produce elastase.

The negative association between AAA and diabetes was initially unexpected, because diabetes is a risk factor for atherosclerosis and because atherosclerosis is associated with AAA, but the strength of the association was not diminished in the second cohort. Several previous studies were found to contain data consistent with this observation, as noted in our earlier report.[2] Since then, 2 more screening studies have reported further supporting evidence. One noted a low prevalence of AAA in a series of older men with diabetes,[10] and the other reported an OR of 0.80 for the association of diabetes with AAA that did not reach statistical significance.[11] Another study[12] observed that among Japanese patients undergoing coronary angiography, those with AAA were significantly less likely to have diabetes. The reasons for the observed negative association remain unclear.[2]

Our findings cast further doubt on a proposed association of AAA with chronic obstructive pulmonary disease. Several studies have reported a univariable association between AAA and chronic obstructive pulmonary disease,[13,14] and similar abnormalities in elastase activity have been observed in the two conditions.[11,12] However, in our first cohort, an association of chronic obstructive pulmonary disease with AAA of 4.0 cm or larger was lost after adjustment for number of years smoked,[2] and a Danish study has since reported similar findings.[15] Data from our second cohort show no association between AAA and chronic obstructive pulmonary disease.

Subjects reporting abdominal imaging (ultrasound, computed tomography, or magnetic resonance imaging) in the past 5 years were less likely to have AAA of 4.0 cm or larger (but not 3.0-3.9 cm) at screening. This finding is of potential interest in the design of future screening programs, and is consistent with our recent similar finding that AAAs detected at a second screening after 4 years tend to be less than 4.0 cm in diameter.[16]

Most associations were stronger for AAA of 4.0 cm or larger than they were for AAA of 3.0 to 3.9 cm. This presumably resulted from the effect of aneurysmal disease severity or from dilution by subjects without true AAA included in the 3.0- to 3.9-cm group. The differences in the ORs were generally small, however, and suggest that using a diameter of 3.0 cm or larger as a cutoff point to define AAA, as has often been done in other studies, probably will not result in important errors.

The findings from this second cohort of veterans undergoing screening for AAA confirm those reported previously from the first cohort. Age, smoking, family history of AAA, and atherosclerotic diseases remained the principal positive associations with AAA, and female sex, diabetes, and black race remained the principal negative associations.

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