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Increased Growth Rate of Abdominal Aortic Aneurysms in Women. The Tromsø Study

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Objectives. *The present study was undertaken in order to assess the effect of gender on the growth rate of abdominal aortic aneurysms (AAAs).*
Methods. *One hundred and eighty-five men and 49 women with AAAs were studied, mean follow-up 62 months, giving 14,544 patient-months of follow-up. A mean of 16 ultrasound examinations was performed on each patient.*
Results. *The mean growth rate was 1.82; 1.65 and 2.43 mm per year in men and women, respectively. In a weighted linear regression analysis, high initial diameter and female gender were independent and significant ($p<0.001$ and $p=0.003$, respectively) predictors for increased growth rate of AAAs. None of the other considered risk factors predicted the growth rate.*
Conclusions. *This is the first study to report a significantly different growth rate of AAAs in females compared to males. It, thus, adds evidence to the view that AAA is a more malignant condition in females than in males and could have implications for the frequency of follow-up in women.*

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Introduction

As early as the 1820s, Sir Asthley Cooper in London observed that aortic aneurysms (AAAs) were four times more prevalent in men than in women. This observation has been confirmed by more recent epidemiological studies.[1–4] Probably, due to this male predominance emphasis has been put on men in discussions and studies concerning AAA and several epidemiological studies have been undertaken with only men included. During the last few years, reports have appeared indicating that AAA in females may be more malignant than in men. Semmens and co-workers have found increased mortality following AAA rupture in women compared to men.[5] Further, increased operative mortality has been observed in both elective and acute surgery for AAA in women[6] and the rupture rate of AAAs has been found higher in women.[7,8] It has been observed that females, as compared with men, have more complications[9] and a higher rate of aborted stentgraft procedures.[10] Women also have a reduced long-term survival after open surgery for AAA.[11]

The risk of rupture of an AAA increases with increasing diameter of the aneurysm.[8] In accordance with a recent Cochrane-review, a maximal diameter of 55 mm or more, or a growth rate of 10 mm or more in 12 months are the common indications for interventional treatment of AAA.[12] However, a fast growth of AAA diameter as indication for repair has recently been questioned.[13] Patients with smaller AAAs, unwillingness for treatment or with serious co-morbidity are followed with serial ultrasound examination of the AAA.

As the maximum diameter of the AAA provides the basis for decisions regarding AAA repair, knowledge of the growth rate of AAAs is important. No previous study has focused on the growth rate of AAA in men compared to in women. The aim of the present report was, therefore, to address whether gender influenced the growth rate of AAA, in a study with 49 women and 185 men with AAA followed for up to 90 months.

All participants in the Tromsø study have signed an informed consent giving their approval for participation in the study and presentation of the results. The local committee for ethics approved the study.

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Materials and Methods

The Tromsø Study started in 1974 and is a population-based study with an emphasis on cardiovascular diseases. The fourth cross-sectional study started in September 1994 and was completed in October 1995 and included a questionnaire and ultrasonographic examination of the abdominal aorta. The detailed protocol for the part of this study regarding AAA has been presented.[4,14]

For the present study, the following information was of interest: all men and women aged 55–74 years and a sample of 5–10 per cent of other age groups in addition to some small subgroups of men and women were eligible for examination.[4] A total of 6892 persons had their abdominal aorta examined with a 3.5 MHz sector probe (Acuson 128-XP). AAA was diagnosed if one or more of the following three criteria was met: (1) a diameter of 35 mm or more at the level of the renal arteries, (2) a localised dilation of the infrarenal aorta or (3) an increase of the infrarenal aortic diameter of 5 mm or more compared to the level of the renal arteries in either transversal or anterior–posterior plane. If AAA or other pathology was found, the patients were referred to the Department of Cardiovascular Surgery and a computed tomography examination of the aorta. A total of 274 men and 74 women were found to have an AAA. Other pathology (e.g. three renal cancers) was found in 24 patients. Eight subjects had both an AAA and other significant pathology. One unrecognised pregnancy also was identified. The indication for surgery in this study was set at an aortic diameter of 55 mm or more.

Of the 348 patients with AAA, 14 did not attend CT-scan or a follow up. Due to the size of the AAA, 31 were operated upon in the initial phase of the study. In 47 persons, the CT-scan revealed non-aneurysmal abdominal aorta. Further, 22 patients with ultrasound detected AAA were either unwilling to participate in follow up, or moved to other parts of the country. The rest, 185 men and 49 women, were eligible for follow up and were followed with ultrasound examination of the abdominal aorta every third or sixth month from inclusion in the study in 1994–1995 to December 31, 2002. No patients withdrew from the study during follow-up. During follow-up, 49 patients were operated due to growth of the AAA and 48 patients died without surgery for their AAA. The follow-up time varied from 3 to 90 months with a mean of 62.4 months (59.6 months for women and 63.2 for men). Seven females and 38 males were followed for the maximum time period of 90 months. The number of ultrasound examinations varied from 2 to 31 with a mean of 16.1 examination (15.3 examinations for women and 16.3 for men). This yielded follow up of 14,544 patient–months with a total of 3773 ultrasound examinations, some performed by a radiologist but mostly by three trained and skilled sonographers. The reproducibility of the ultrasonographic examinations during the screening has been published.[14] Two of the three sonographers, using the same ultrasound machines as used for screening, performed the measurements of the AAAs in the follow-up study. The diameter of the AAAs as measured in the screening is used as the initial diameter for the present study.

The data were stored in an Access database. Calculations and organisation of the data were performed in Excel spreadsheet. Statistical calculations were performed in SAS and SPSS statistical packages. The change in diameter was assumed to be linear over time and modelled using ordinary linear regression analysis. The change in the diameter of the aneurysm for each person was estimated as the regression coefficient using time as the independent variable and diameter of AAA as the dependent variable. The time unit was set to 3 months, and this growth rate was then multiplied with four to give growth rate in mm per year. For the main analysis, a multiple regression analysis was performed. In a linear regression analysis, growth rate was the dependent variable and age, gender and start diameter as well as other risk factors for cardiovascular diseases were the independent variables. The analysis was weighted with the number of observations for each patient. When comparing means, *t*-test was performed and different variance between the groups was assumed. When comparing proportions Fisher's exact test was performed. Wilcoxon's rank test was used for non-parametric comparison of groups.

Results

The characteristics of the patients at the start of the follow-up period are given in Table 1. Adjustment for age did not notably change the *p*-values for the comparisons of men and women with AAAs (data not shown).

The overall mean growth rate (and standard deviation) was 1.82 (2.10) mm per year. The highest value was 16.0 mm per year. As shown in Table 2, the mean growth rate was 0.58 mm per year for AAAs with an initial diameter <25 and 2.63 mm for AAAs with initial diameter >49 mm.

The mean growth rate (and standard deviation) for women and men were 2.43 (2.95) and 1.65 (1.78) mm per year, respectively. The growth rates for both genders at the different levels of initial diameter are

Table 1. The characteristics of the patients at the start of the study

	Females	Males	*p*-value
N	49	185	
Initial age (years)	69.1 (5.6)	66.4 (6.3)	0.005
Mean initial diameter of AAA (mm)	31.9 (7.0)	35.5 (7.4)	0.002
Median initial diameter (min–max)	31 (22–55)	34 (25–85)	0.002
Systolic blood pressure (mmHg)	158.8 (25.2)	148.3 (21.8)	0.010
Diastolic blood pressure (mmHg)	85.7 (13.6)	86.2 (13.0)	0.9
Total cholesterol (mmol/l)	7.62 (1.30)	6.77 (1.15)	<0.001
HDL-cholesterol (mmol/l)	1.51 (0.43)	1.26 (0.33)	<0.001
Height (cm)	160.6 (4.6)	174.7 (6.8)	<0.001
Weight (kg)	67.0 (12.3)	81.6 (12.6)	<0.001
Body-mass index	26.0 (4.6)	26.7 (3.8)	0.3
Daily smokers	35/49 (71.4%)	88/184 (47.6%)	0.004
Angina pectoris	12/49 (24.5%)	53/184 (28.8%)	0.6
Cardiac infarction	7/49 (14.3%)	40/183 (21.9%)	0.3

The information is given as mean (and standard deviation), median or as proportions and percentages.

shown in Fig. 1. In the regression analysis, initial diameter and gender were both independent and significant predictors for the growth rate. Adjusted for age and initial diameter, the mean annual growth rate was 0.7 mm lower in men than in women ($p=0.003$), and adjusted for age and gender, the mean annual growth rate was 0.7 mm higher when the initial diameter increased 10 mm ($p<0.001$). Age at screening was not a significant predictor of the growth rate. The other characteristics and risk factors were also tested, but none was significant predictors for growth rate when start diameter, age and gender were included in the model.

For 10 patients, all men, the estimated growth rate was negative. The median initial diameter for these was 32.5 (31–52) mm. The median growth rate for these 10 patients was −0.38 (−8.0 to −0.03) mm per year. The lowest value was calculated in a patient with an AAA of 52 mm at the first examination, and after 3 months the diameter was assessed to be 50 mm. The patient expressed a preference for surgery and was not eligible for further measurements. In all the calculations and presentations in this paper, these 10 patients with a negative growth rate were included. Exclusion of these 10 patients did not alter significantly the results (data not shown).

The mean initial AAA diameter was 31.9 and 35.5 mm for women and men, respectively (Table 1). In the cross-sectional study,[4] the mean aortic diameter in 1370 females in the age group 65–74 years was 19.8 mm, and for the 1117 males in the same age group it was 23.7 mm. Thus, the initial diameter of the AAAs in the present study are 1.61 and 1.50 times greater in, women and men, respectively, than the mean diameter for this age group in the general population.

Discussion

To our knowledge, this is the first study examining formally the growth rates of AAA according to gender. Even if the number of females in the groups with the largest initial diameter was low, the difference between the growth rates according to gender was pronounced and highly significant. This study also confirms earlier findings that larger diameter AAAs grow faster.[15–17]

There are some reservations related to the methods used in this study. The calculations giving the growth rate in each patient assumes a linear growth of the aneurysms, whereas the growth of AAAs is exponential. Our results show that, the growth rate increases

Table 2. The mean growth rate (mm per year (standard deviation)) of the 234 AAAs according to start-diameter and gender

	All	Maximal diameter of aorta at start of follow-up						
		<25	25–29	30–34	35–39	40–44	45–49	>49
All								
Mean (SD)	1.82 (2.10)	0.58 (0.54)	1.19 (0.97)	1.80 (2.32)	1.75 (1.10)	2.31 (2.30)	3.36 (3.16)	2.63 (4.70)
N	234	3	43	87	58	23	11	9
Females								
Mean (SD)	2.43 (2.95)	0.58 (0.54)	1.47 (1.33)	2.75 (3.82)	2.01 (1.17)	5.94 (3.09)	7.01 (7.06)	6.80 (–)
N	49	3	17	15	9	2	2	1
Males								
Mean (SD)	1.65 (1.78)	–	1.01 (0.59)	1.60 (1.84)	1.70 (1.09)	1.96 (1.97)	2.55 (1.48)	2.11 (4.74)
N	185	0	26	72	49	21	9	8

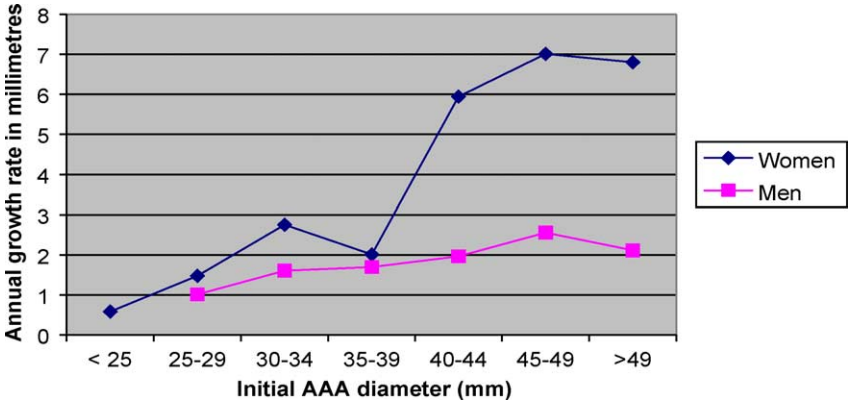

Fig. 1. The growth rate of AAA in 49 women and 185 men followed up to 90 months. In a regression analysis, both initial AAA diameter and female gender predicted the growth rate ($p<0.001$ and $p=0.003$, respectively).

with the diameter of the AAA. However, few patients had such high initial AAA diameter that the exponential and linear curves differed significantly. A relatively larger AAA in women compared to men could underlie the increased AAA growth rate observed in women. The mean diameter of the AAAs in the females was 1.61 times larger than the mean infrarenal aortic diameter in the normal population. In the males the diameter was 1.50 times higher. This difference is negligible and is unlikely to explain the difference in growth rate between the two genders. It also may be a cause of concern that we have only followed 234 of the 348 subjects who had an AAA diagnosed. However, the group of subjects who were followed did not differ significantly from the other subjects with regard to age or sex (data not shown). Most likely, the 10 negative values for growth rate in this cohort were the result of errors in the measurements.

The percentage of patients found to have an AAA in population studies varies with age and sex distribution of the population and the diagnostic criteria for inclusion, e.g. the diameter of the aorta.[4] The AAA growth rate also appears to depend on these same factors. In 1993, Bengtsson and co-workers found a growth rate of 3.1 mm per year and increased growth with increased diameter. Their study was based on 155 subjects with an AAA, 20–80 mm in diameter with both men and women included.[15] Similar growth rates and a correlation with growth rate and diameter has been confirmed in other studies.[17,18] Santilli and co-workers found a growth rate of 1.6 mm per year in men with initial AAA diameter of 30–39 mm.[17] This finding is identical with that for the same subgroup in our results (Table 2). Association of AAA growth rate with cardiac disease,[19] age and a history of cigarette smoking have been found.[18,20] In the present study, the participants' information on daily smoking at the start of the study did not predict the growth rate of the AAA. Stopping smoking has been found to reduce the growth.[21] We do not have information about smoking during the follow-up study.

The main finding of the present study; that AAA grow faster in women, adds evidence to the view that AAAs are more malignant in females than in men. This could have implications for AAA screening policies. Surveillance might need to be more frequent in women, compared with men, with an AAA diameter of more than 40 mm. However, we acknowledge that the number of women included in our study was low, and believe that our results ought to be confirmed in larger studies. However, since treatment of the AAAs in women may have more complications and a higher mortality than in men, there may be no indication for earlier intervention in women.

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References

1 Scott RA, Ashton HA, Kay DN. Abdominal aortic aneurysm in 4237 screened patients: prevalence, development and management over 6 years. *Br J Surg* 1991;**78**:1122–1125.
2 Simoni G, Pastorino C, Perrone R, Arida A, Gianrossi R, Decian F, Cittandini Jr G, Baiardi A, Bachi V. Screening for abdominal aortic aneurysms and associated risk factors in a general population. *Eur J Vasc Endovasc Surg* 1995;**10**:207–210.
3 Pleumeekers HJ, Hoes AW, van der Does E, van Urk H, Hofman A, de Jong PT, Grobbee DE. Aneurysms of the abdominal aorta in older adults. The Rotterdam study. *Am J Epidemiol* 1995;**142**:1291–1299.
4 Singh K, Bønaa KH, Jacobsen BK, Bjørk L, Solberg S. Prevalence of and risk factors for abdominal aortic aneurysms

in a population-based study. The Tromsø study. *Am J Epidemiol* 2001;**154**:236–244.
5 Semmens JB, Norman PE, Lawrence-Brown MM, Holman CD. Influence of gender on outcome from ruptured abdominal aortic aneurysm. *Br J Surg* 2000;**87**:191–194.
6 Dimick JB, Stanley JC, Axelrod DA, Kazmers A, Henke PK, Jacobs LA, Wakefield TW, Greenfield LJ, Upchurch Jr GR. Variation in death rate after abdominal aortic aneurysmectomy in the United States. Impact of hospital volume, gender, and age. *Ann Surg* 2002;**235**:579–585.
7 The UK Small Aneurysm Trial Participants. Long-term outcomes of immediate repair compared with surveillance for small abdominal aortic aneurysms. *N Engl J Med* 2002;**346**:1445–1452.
8 Brown PM, Zelt DT, Sobolev B. The risk of rupture in untreated aneurysms: the impact of size, gender, and expansion rate. *J Vasc Surg* 2003;**37**:280–284.
9 Wolf YG, Arko FR, Hill BB, Olcott 4th C, Harris Jr EJ, Fogarty TJ, Zarins CK. Gender differences in endovascular abdominal aortic aneurysm repair with the AneuRx stent graft. *J Vasc Surg* 2002;**35**:882–886.
10 Mathison M, Becker GJ, Katzen BT, Benenati JF, Zemel G, Powel A, Kovacs ME, Lima MM. The influence of female gender on the outcome of endovascular abdominal aortic aneurysm repair. *J Vasc Interv Radiol* 2001;**12**:1047–1051.
11 Stenbaek J, Granath F, Swedenborg J. Outcome after abdominal aortic aneurysm repair. Difference between men and women. *Eur J Vasc Endovasc Surg* 2004;**28**:47–51.
12 Ballard DJ, Fowkes FG, Powell JT. Surgery for small asymptomatic abdominal aortic aneurysms. *Cochrane Database Syst Rev*22000;:CD001835.
13 Sharp MA, Collin J. A myth exposed: fast growth in diameter does not justify precocious abdominal aortic aneurysm repair. *Eur J Vasc Endovasc Surg* 2003;**25**:408–411.
14 Singh K, Bønaa KH, Solberg S, Sørlie D, Bjørk L. Intra- and interobserver variability in ultrasound measurements of abdominal aortic diameter. The Tromsø Study. *Eur J Vasc Endovasc Surg* 1998;**15**:497–504.
15 Bengtsson H, Bergquist D, Ekberg O, Ranstam J. Expansion pattern and risk of rupture of abdominal aortic aneurysms that were not operated on. *Eur J Surg* 1993;**159**:461–467.
16 Stonebridge PA, Draper T, Kelman J, Howlett J, Allan PL, Prescott R, Ruckley CV. Growth rate of infrarenal aortic aneurysms. *Eur J Vasc Endovasc Surg* 1996;**11**:70–73.
17 Santilli SM, Littooy FN, Cambria RA, Rapp JH, Tretinyak AS, d'Audiffret AC, Kuskowski MA, Roethle ST, Tomczak CM, Krupski WC. Expansion rates and outcome for the 3.0 cm to the 3.9 cm infrarenal abdominal aortic aneurysm. *J Vasc Surg* 2002; **35**:666–671.
18 Chang JB, Stein TA, Liu JP, Dunn ME. Risk factors associated with rapid growth of small abdominal aortic aneurysms. *Surgery* 1997;**121**:117–122.
19 Englund R, Hudson P, Hanel K, Stanton A. Expansion rates of small abdominal aortic aneurysms. *Aust N Z J Surg* 1998;**68**:21–24.
20 Brady AR, Thompson SG, Fowkes FG, Greenalgh RM, Powell JT. UK small aneurysm trial participants. *Circulation* 2004;**110**:16–21.
21 MacSweeney ST, Ellis M, Worrell PC, Greenalgh RM, Powell JT. Smoking and growth rate of small abdominal aortic aneurysms. *Lancet* 1994;**334**:651–652.

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