CARDIOVASCULAR DISEASE

Abdominal aortic aneurysms, or a relatively large diameter of non-aneurysmal aortas, increase total and cardiovascular mortality: the Tromsø study

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Background In a population-based study in Tromsø, Norway, the authors assessed whether an abdominal aortic aneurysm (AAA) or the maximal infrarenal aortic diameter in a non-aneurismal aorta influence total and cardiovascular disease (CVD) mortality.

Methods A total of 6640 men and women, aged 25–84 years, were included in a 10-year mortality follow-up: 345 subjects with a diagnosed AAA and 6295 subjects with a non-aneurismal aorta. Non-aneurismal aortic diameter and prevalent AAAs were categorized into seven groups.

Results In subjects without an AAA, an aortic diameter ⩾30 mm increased age- and sex-adjusted total mortality [mortality rate ratio (MRR) = 3.73, 95% confidence interval (CI) 1.77–7.89] and CVD mortality (MRR = 9.24, 95% CI 4.07–20.97) compared with subjects with aortic diameter of 21–23 mm. An AAA at screening was strongly associated with deaths from aortic aneurysm and was associated with total (MRR = 1.60, 95% CI 1.31–1.96) and CVD mortality (MRR = 2.41, 95% CI 1.81–3.21). This was not explained by deaths due to an AAA. Adjustments for CVD risk factors could fully explain the increased total, but not CVD mortality in subjects with an AAA.

Conclusions An AAA increases total and CVD mortality. In the large majority of subjects with a non-aneurysmal aorta, the diameter does not influence total or CVD mortality. However, in individuals with a maximal diameter >26 mm (2% of the population), a positive relationship is found.

Keywords Epidemiology, prospective cohort study, abdominal aortic aneurysm, total mortality, cardiovascular mortality, ultrasonography

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Introduction

An abdominal aortic aneurysm (AAA) is usually an asymptomatic condition, but with high mortality rate related to rupture.[1–3] The disease is the cause of deaths in 1–2% of all deaths in the Western world.[3,4] The risk of AAA rupture has been evaluated in long-term follow-up both in clinical and epidemiological settings. In subjects with an AAA, increasing diameter predicts total mortality.[5–8] However, few prospective studies[7,8] have investigated relationships between the diameter of the non-aneurismal aorta and risk factors for total and cardiovascular disease (CVD) mortality.

We have studied the long-term (10 years) consequences in terms of mortality of having an AAA diagnosed in a community-based screening programme and whether an increasing maximal aortic diameter in a non-aneurismal aorta influences total mortality and CVD mortality.

Materials and Methods

In the fourth Tromsø study (1994–95), a total of 3394 men and 3498 women (79% of the eligible population), aged 25–84 years, were examined by ultrasound in order to measure the maximal diameter of the infrarenal aorta and to assess the prevalence of AAAs.[9]

Questionnaires, physical measurements and blood samples

The survey included self-administered questionnaires concerning physical activity in leisure, smoking habits and antihypertensive medication. Leisure time physical activity was categorized into three groups: low, medium and high. Low physical activity means that the subjects were never so active during their leisure time that they were sweating or out of breath and that they had been lightly active only (not sweating or out of breath) for <1 h/week during the past year. Subjects with high physical activity reported high activity (sweating or out of breath) at least 1 h/week.

Smoking was categorized into seven groups: never-smokers, ex-smokers (<10 years cessation, 10–19 years cessation and ≥20 years cessation) and current smokers (less than 10 cigarettes/day, 10–19 cigarettes/day and 20 cigarettes or more/day).

Standardized measurements of height, weight, waist, hip and blood pressure were carried out.[9] Hypertension was defined as systolic blood pressure >160 mmHg or diastolic blood pressure >95 mmHg, or ever use of antihypertensive medication. Serum total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides fibrinogen, creatinine and glycated haemoglobin (HbA$_{1c}$) were analysed as detailed elsewhere.[9] Estimated glomerular filtration rate (eGFR) was calculated.[10] The analyses were done at the Department of Clinical Chemistry, University Hospital of North Norway.

Abdominal aorta ultrasound measurements

The ultrasound examination was carried out with an Acuson, 128 XP B-mode Doppler (Acuson Corporation, Mountain View, CA, USA) with a 3.5-MHz sector probe.

The ultrasonographic measurements were performed by one of six persons.[9] Aortic diameters at the level of the renal arteries, 1 cm distal to this level, the bifurcation and the maximal infrarenal aortic diameter were measured. Both transversal and anterior–posterior diameters were measured. In the present analyses, the maximal infrarenal aortic diameter was defined as the mean of the maximal transversal and anterior–posterior diameters.

The inter- and intra-observer variability of the ultrasound examination has been reported previously.[11] The difference between two measurements (both inter- and intra-observer agreement) of the maximal aortic diameter were ⩽4 mm in 95% of the pairs.

An AAA was considered present if one or more of the following criteria were met: (i) the aortic diameter at the level of renal arteries was ⩾35 mm in either the anterior–posterior or the transverse plane; (ii) the infrarenal aortic diameter in either plane was ⩾5 mm larger than the diameter of the level of renal arteries; or (iii) a localized dilatation of the aorta was present on ultrasound. The criteria for the diagnosis of an AAA were set to give a high sensitivity for finding an AAA. Seventy-five percent of the AAAs were based on a ⩾5-mm increase in the diameter from the renal level.[9] If an AAA was diagnosed, the patients were referred to the Department of Cardiovascular Surgery, University Hospital of North Norway.

Study population

A total of 6798 men and women had ultrasound examination data of sufficient quality to reveal whether an AAA was presented or not and gave consent for follow-up. However, the maximal infrarenal diameter was not measured accurately in 135 subjects. We also excluded 23 subjects who had a prosthetic graft in the abdominal aorta. The analyses were therefore limited to 3387 men and 3253 women.

Follow-up

The official personal registration number served as a unique identification of each person, linking our data from the ultrasound screening to information on vital status and cause of death obtained from files kept at Statistics Norway, Oslo. Follow-up started the day they attended the screening. Subjects who were alive at the end of follow-up were censored on 31 December 2005. Emigrants were censored the day they left Norway. The following end-points were considered: total mortality, CVD mortality including

sudden death [International Statistical Classification of Diseases and Related Health Problems (ICD)-9: 390–459, 798.0, ICD-10: I00–I99, R95] and mortality due to aortic aneurysm and/or aortic dissection (ICD-9: 441, ICD-10: I71). In the following, the latter group is referred to as deaths due to aortic aneurysm. The mean follow-up period was 10.1 years (range 0.1–11.3 years).

Statistical analysis

Unadjusted associations between a number of considered risk factors and death during follow-up were analysed by using analysis of variance and cross-tabulations. In separate analyses, the *P*-values for the same associations were adjusted for age and sex by analysis of covariance and Mantel–Haenszel methods. The main independent variable included information about the diameter of the non-aneurismal diameter categorized into six groups: <18, 18–20,

21–23, 24–26, 27–29 and 30–34 mm, and prevalent AAAs as the seventh group. The reference category 21–23 mm was chosen because it includes the highest number of deaths.

Relationships between the presence of an AAA or the maximal infrarenal diameter in the non-aneurismal aorta, respectively, and mortality rates were investigated in a Cox proportional hazards regression model using time in study as the time variable. The variables included in the multivariate model were those of the variables included in Table 1 found to be associated with total or CVD mortality in this cohort with a *P*-value ≤ 0.05 when age, sex and the main independent variable (which conveys information about aortic diameter and the presence of an AAA) was taken into account. These variables were: smoking, body mass index (BMI), physical activity in leisure, systolic blood pressure, serum total and HDL cholesterol, serum triglycerides, glycated haemoglobin, plasma fibrinogen, waist/hip ratio, hypertension,

Table 1 Baseline characteristics of subjects who survived or died during follow-up (Tromsø; Norway, 1994–95)

Risk factor	Survivors ($n = 5540$)	Dead ($n = 1100$)	*P*
Male sex (%)	46.5	61.5	<0.001
Age (years)	58.9 (10.2)	66.5 (7.0)	<0.001
BMI (kg/m^2)	26.0 (3.8)	26.0 (4.4)	0.73
Waist-to-hip ratio	0.86 (0.08)	0.90 (0.09)	<0.001
Systolic blood pressure (mmHg)	143.3 (21.8)	153.4 (24.1)	<0.001
Diastolic blood pressure (mmHg)	82.8 (12.5)	86.2 (14.2)	<0.001
Hypertensive (%)	32.0	53.5	<0.001
Leisure physical activity			
Low (%)	19.6	30.7	
Medium (%)	57.7	54.8	<0.001
High (%)	22.7	14.5	
Smoking			
Never smoked (%)	33.5	21.9	
Ex-smoker (%)	35.7	36.6	<0.001
Current smoker (%)	30.9	41.6	
Serum total cholesterol (mmol/l)	6.74 (1.29)	6.80 (1.34)	0.16
Serum HDL cholesterol (mmol/l)	1.55 (0.43)	1.49 (0.43)	<0.001
Serum triglycerides (mmol/l)	1.67 (1.05)	1.81 (1.13)	<0.001
Glycated hemoglobin (HbA$_{1c}$) (%)	5.43 (0.57)	5.68 (0.93)	<0.001
Plasma fibrinogen (mmol/l)	3.32 (0.81)	3.73 (0.97)	<0.001
eGFR[a]	93.2 (18.1)	90.9 (20.4)	<0.001
Prevalent CVD at baseline (%)	11.1	28.6	<0.001
Use of lipid-lowering drugs (statins)	1.6	1.3	0.5
Diabetes (%)	2.0	8.6	<0.001
Maximal abdominal aortic diameter (mm)	20.9 (4.1)	23.1 (6.8)	<0.001
AAA present (%)	3.9	11.8	<0.001

The number may vary somewhat due to missing information.
[a]The Modification of Diet in Renal Disease equation.[10]

eGFR, prevalent self-reported CVD (previous myocardial infarction, angina pectoris or stroke) or diabetes mellitus. Ninety-five percent confidence intervals (CIs) were calculated. The P-values were two-sided throughout. All analyses were performed using the SAS package.

Results

Out of the 6640 subjects included in the analyses, 676 men and 424 women died during follow-up (16 deaths per 1000 person-years). A total of 471 (7.1%) subjects died because of CVDs, 27 (0.4%) of them with an aneurysm as the underlying cause of death.

Table 1 displays baseline data for the population according to whether they died during follow-up or not. The two groups differed with regard to a number of variables and adjustment for age and sex did not change these conclusions except for the relationship with HDL-cholesterol.

The aneurysms included in our study were relatively small as only 7% had a maximal diameter >50 mm and 82% had a diameter <40 mm. Thirty-three percent (113 subjects) had a diameter <30 mm. Seventy-nine percent of the AAA cases were men, 92% were ever smokers and 58% were hypertensive. The characteristics of subjects with an AAA (mean values) were: 66.1 years, BMI 26.6 kg/m^2, systolic blood pressure 153 mmHg, serum total cholesterol 6.9 mmol/l, HDL-cholesterol 1.33 mmol/l and maximal aortic diameter 34.9 mm.

The mean maximal diameter (standard deviation) in non-aneurismal aortas was 20.5 (2.7) mm with the range of 11–34 mm. Approximately 4% of the men and 24% of the women had a maximal aortic diameter <18 mm.

AAA mortality

Out of the 345 subjects with an AAA diagnosed at screening, 20 (6%) died due to aortic aneurysm, whereas 7 (0.1%) of the 6295 subjects without an AAA diagnosed died due to aortic pathology. However, five out of these seven subjects died because of aortic dissection or a thoracic aneurysm, and two died because of an AAA. The age- and sex-adjusted risk of dying due to an aortic aneurysm was 36 (95% CI 14–89) times higher in subjects with AAA diagnosed at screening compared with those without an AAA. The relationship was seemingly stronger in women, but the P-value for the difference between the genders was 0.15 (results not shown).

Total mortality

A higher age- and sex-adjusted mortality was found in subjects with a maximal diameter 30–34 mm compared with subjects with maximal diameter 21–23 mm [mortality rate ratio (MRR) = 3.73, 95% CI 1.77–7.89]

(Table 2). Subjects with an AAA at baseline had 1.6 times higher total mortality than subjects with maximal diameter 21–23 mm (MRR = 1.60, 95% CI 1.31–1.96). The mortality in subjects with non-aneurismal aorta with diameter 30–34 mm was higher than in subjects with an AAA diagnosed at baseline (MRR = 2.33, 95% CI 1.09–5.00).

A test for interaction by sex indicated that the association for total mortality was different in men and women (P = 0.02 for interaction). However, total mortality was associated with a non-aneurismal aorta with diameter 30–34 mm and with an AAA diagnosed at baseline in both genders. Furthermore, an interaction was also suggested for age (P = 0.05), but the same association emerged in older (aged ≥70 years at start of follow-up) as in younger subjects. A non-aneurismal aorta with diameter 30–34 mm seems nevertheless to be a stronger risk factor in older subjects (results not shown in Table 2). It is, however, difficult to evaluate these possible interactions due to the paucity of cases.

Adjustment of the relationship between the maximal aortic diameter, prevalent AAA and total mortality for possible confounders only marginally influenced the relationship with a large non-aneurismal diameter (30–34 mm), but the relationship with an AAA at baseline was completely explained by these adjustments (results not shown in Table 2).

In a separate set of analyses, we excluded the 27 deaths attributed to aortic aneurysm from the data set, thus limiting the analyses to 1073 deaths in 6613 subjects. The relationship between the presence of an AAA at baseline and total mortality was upheld (MRR = 1.41, 95% CI 1.14–1.75).

CVD mortality

A strong, exponential relationship was found between maximal diameter and CVD mortality (Table 2). Compared with subjects with maximal aortic diameter in the 21–23 mm range, an increased CVD mortality was found both for subjects with maximal diameter 27–29 mm (MRR = 1.92, 95% CI 1.16–3.19) and particularly when the maximal diameter was 30–34 mm (MRR = 9.24, 95% CI 4.07–20.97). In the latter group, there were 6 deaths in 16 subjects [stroke (2 persons), ischaemic heart disease (3 persons) and rupture of a thoracic aortic aneurysm (1 person)]. An AAA at baseline increased age- and sex-adjusted CVD mortality by ~2.5-fold compared with subjects with the reference category (MRR = 2.41, 95% CI 1.81–3.21). The CVD mortality in subjects with non-aneurismal aorta with diameter 30–34 mm was significantly higher than in subjects with an AAA at baseline (MRR = 3.83, 95% CI 1.66–8.83).

We found no interaction by sex, but an interaction was found for age (P = 0.01). However, in both individuals aged <70 years at baseline and in older subjects, we found positive relationships with non-aneurismal aorta with diameter 30–34 mm and with

Table 2 Age-and sex-adjusted total and cardiovascular mortality in a 10-year follow-up according to maximal infrarenal aortic diameter (millimetres) in subjects with non-aneurysmal aortas and subjects with AAAs (Tromsø; Norway, 1994–2005)

Aortic diameter	Subjects (*n*)	Total mortality		CVD mortality		Total mortality		CVD mortality	
		Deaths (*n*)	%	Deaths (*n*)	%	MRR	95% CI	MRR	95% CI
<18 mm	930	101	10.9	43	4.6	1.06	0.84–1.33	1.21	0.84–1.74
18–20 mm	2538	329	13.0	139	5.5	0.93	0.80–1.09	1.07	0.84–1.37
21–23 mm	2082	362	17.4	132	6.3	1.00	Ref.	1.00	Ref.
24–26 mm	632	140	22.2	58	9.2	1.05	0.86–1.27	1.17	0.86–1.60
27–29 mm	97	31	32.0	17	17.5	1.34	0.93–1.94	1.92	1.16–3.19
30–34 mm	16	7	43.8	6	37.5	3.73	1.77–7.89	9.24	4.07–20.97
Prevalent AAAs	345	130	37.7	76	22.0	1.60	1.31–1.96	2.41	1.81–3.21
Total	6640	1100	16.6	471	7.1				

the presence of an AAA at baseline on one hand, and CVD mortality on the other.

Further adjustment of the association between maximal diameter and CVD mortality for possible confounders only marginally influenced the relationship. If anything, the point estimate for subjects with maximal diameter 30–34 mm was increased. The relationship with an AAA at baseline, however, was attenuated somewhat (MRR = 1.74, 95% CI 1.28–2.35, based on 446 deaths in 6334 subjects).

After excluding 27 deaths ascribed to aortic aneurysm, there were 444 deaths in the population due to CVDs during follow-up. However, even after excluding this particular type of CVD death, an AAA at baseline was a risk factor for CVD mortality (MRR = 1.86, 95% CI 1.36–2.55).

Some other studies define an AAA as a maximal infrarenal diameter ⩾30 mm. Applying this definition for an AAA gave results very similar to those presented in Table 2 (see also Table 3). Compared with subjects with maximal diameter 21–23 mm, subjects with an AAA defined as maximal diameter ⩾30 mm had 1.8 and 2.8 times higher total and CVD mortality, respectively. In Table 2, the corresponding figures were 1.6 and 2.4.

Alternatively, if one choose to consider an aorta with a maximal diameter 30–34 mm as an AAA and merge these 16 subjects with diameter in the 30–34 mm bracket with the persons with a diagnosed AAA according to our definition (Table 2), the point estimates for the mortality in subjects with an AAA are only slightly increased compared with those presented in Table 2 (results not shown).

Discussion

In this 10-year follow-up of 6640 subjects, we found that both a prevalent AAA and a relatively large maximal infrarenal diameter in non-aneurismal aortas increased total mortality and CVD mortality. Few studies[7] have been able to evaluate the mortality according to aortic diameter in the full range

from the relatively narrow to the ectatic aorta, including AAAs.

The strong association between the presence of an AAA and dying of aortic aneurysm was, of course, an expected finding.[2,8,12–15] Some studies have suggested that an AAA has worse prognosis in women,[16–18] and our results tend to support this, but there were too few cases in our study to test this hypothesis.

Subjects with an AAA have increased CVD mortality. This is in accordance with previous studies.[5–8] We had expected, however, that individuals with an AAA at baseline would have a higher mortality than subjects with a non-aneurismal aorta with diameter in the 30–34 mm range. It is not clear whether treatment or changes in lifestyle partly can account for our findings. Approximately 25% of the subjects with an AAA have been subject to open surgery or endovascular repair of the abdominal aorta during follow-up. As elective intervention has low mortality compared with if the aneurysm ruptures, this will reduce the relationship between AAA and mortality compared with in a population without any intervention. The exclusion of the subjects with an AAA who received open surgery or endovascular repair from the analysis did not influence our findings, however.

As in most prospective studies, including this one, it is possible that the subjects who are followed up have changed risk factors after the baseline data were collected. Subjects with a known AAA must be expected to be motivated to change risk factor levels. Thus, risk factor levels may have been reduced more systematically in subjects with an AAA than in other subjects. Indeed, unpublished data from the subgroup of subjects who attended both the baseline screening and a similar screening 7 years later[19] indicate that individuals with an AAA at the baseline had a somewhat higher rate of quitting smoking and larger reduction in serum cholesterol than individuals without an AAA (both $P \leqslant 0.002$).

A maximal diameter 30–34 mm in non-aneurismal aortas increased total and particularly CVD mortality (Table 2). Our results thus support that a large

Table 3 Age- and sex-adjusted total and CVD mortality in a 10-year follow-up according to maximal infrarenal aortic diameter (millimetres) (Tromsø; Norway, 1994–2005)

Aortic diameter	Subjects (*n*)	Total mortality		CVD mortality		Total mortality		CVD mortality	
		Deaths (*n*)	%	Deaths (*n*)	%	MRR	95% CI	MRR	95% CI
<18 mm	930	101	10.9	43	4.6	1.05	0.83–1.32	1.18	0.82–1.69
18–20 mm	2539	329	13.0	139	5.5	0.93	0.79–1.08	1.05	0.82–1.34
21–23 mm	2086	364	17.5	134	6.4	1.00	Ref.	1.00	Ref.
24–26 mm	671	151	22.5	63	9.4	1.07	0.89–1.30	1.20	0.89–1.62
27–29 mm	167	53	31.7	29	17.4	1.31	0.98–1.75	1.86	1.24–2.78
⩾30 mm	246	101	41.1	62	25.2	1.77	1.41–2.21	2.79	2.05–3.79
Total	6639	1099	16.6	471	7.1				

diameter is associated with general atherosclerosis.[8,20,21] A large non-aneurismal aorta with a thrombotic mass could be basis for thrombotic embolism and subsequent morbidity and mortality. Subjects with an aortic diameter of ⩾27 mm could be considered as subject for further follow-up, not only because they may be at risk of developing an aneurysm,[14,22,23] but also as they are at high risk of dying because of CVDs other than AAA.

In accordance with the findings of Norman *et al.*,[7] there were indications of a somewhat increased CVD mortality in subjects with a low aortic diameter (<18 mm) (MRR = 1.21, 95% CI 0.84–1.74) (Table 2). A recent study by Johnsen *et al.*[24] concluded that the lumen diameter of common carotid artery (CCA) is positively correlated with the abdominal aortic diameter and femoral aortic diameter as well as an independent risk factor for AAA. Thus, a low aortic diameter may be correlated with narrow arteries in general, including the coronary arteries. It is likely that atherosclerosis and thrombosis in a narrow artery will give clinical consequences earlier than in a wide artery. However, the relative low number of CVD deaths in this group with a narrow aorta precludes further investigation of this finding.

Some other studies have used a simpler definition of an AAA, e.g. a maximal infrarenal diameter ⩾30 mm.[25] The definition used in this study has been applied in a number of papers based on the same dataset.[9,19,24,26] The concordance between the two ways of classifying an AAA was substantial with a κ-value[27] of 0.77 (95% CI 0.73–0.81). Our definition of an AAA permits an aorta with maximal diameter of ⩾30 mm to be considered non-aneurismal. However, the results with regard to the mortality in subjects with an AAA are robust to the way an AAA is diagnosed: we find increased total and CVD mortality in subjects with an AAA. This is true whether we apply our complicated definition, or merge subjects who fulfil this definition of an AAA with the 16 subjects with maximal aortic diameter 30–34 mm who did not, or, finally, simply regard any aorta with maximal diameter ⩾30 mm as an AAA.

The strength of this study is that it is population based, not based on in-patients or other selected subjects. The attendance rate to the baseline study was high (79% of the eligible population) and we have a complete follow-up with regard to mortality. The limitations are mainly related to misclassification. A few AAAs may have been overlooked in 1994 and included in the group of subjects without AAAs. This has underestimated the true strength of the relationship between AAA and total as well as cause-specific mortality. Misclassification of the aortic diameter has also attenuated the associations between aortic diameter and mortality.

We base our results with regard to the cause specific mortality (aortic pathology or CVDs in general) on the cause of death registered on the death certificate. Sudden deaths are included in CVD deaths in our analyses. Some misclassification with regard to cause of death has undoubtedly taken place. Only 21% of the diagnosis of CVD death was based on autopsy. The corresponding figure for deaths due to an aneurysm was 44%. Aorta dissection has another aetiology than aneurysms. There were only four deaths caused by aortic dissection, however. Some aneurysms are due to connective tissue disorders (e.g. Marfan's syndrome). These disorders have low prevalence (typically 4–6/100 000[28]), however, and cannot have influenced our conclusions.

In summary, we find that an AAA increases total and CVD mortality. Furthermore, in the large majority (98%) of subjects with a non-aneurismal aorta, the diameter does not influence total or CVD mortality. However, in individuals with a maximal diameter >26 mm (2% of this population), a positive relationship is found. The associations with total and CVD mortality were weaker in the group of AAA patients. The reason for this is not completely understood, but probably includes surgical or endovascular intervention, medical treatment and life-style modification.

Funding

KEY MESSAGES

- An AAA increases total and CVD mortality.

- A non-aneurysmal aorta with a maximal diameter >26 mm increases total and CVD mortality.

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