

Systematic review and meta-analysis of growth rates of small abdominal aortic aneurysms

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Background: Small abdominal aortic aneurysms are usually asymptomatic and managed safely in ultrasound surveillance programmes until they grow to a diameter threshold where intervention is considered. The aim of this study was to synthesize systematically the published data on growth rates for small aneurysms to investigate the evidence basis for surveillance intervals.

Methods: This was a systematic review of the literature published before January 2010, which identified 61 potentially eligible reports. Detailed review yielded 15 studies providing growth rates for aneurysms 3.0–5.5 cm in diameter (14 in millimetres per year, 1 as percentage change per year). These studies included 7630 people (predominantly men) enrolled during 1976–2005.

Results: The pooled mean growth rate was 2.32 (95 per cent confidence interval 1.95 to 2.70) mm/year but there was very high heterogeneity between studies; the growth rate ranged from –0.33 to +3.95 mm/year. Six studies reported growth rates by 5-mm diameter bands, which showed the trend for growth rate to increase with aneurysm diameter. Simple methods to determine growth rate were associated with higher estimates. Meta-regression analysis showed that a 10-mm increase in aneurysm diameter was associated with a mean(s.e.m.) 1.62(0.20) mm/year increase in growth rate. Neither mean age nor percentage of women in each study had a significant effect. On average, a 3.5-cm aneurysm would take 6.2 years to reach 5.5 cm, whereas a 4.5-cm aneurysm would take only 2.3 years.

Conclusion: There was considerable variation in the reported growth rates of small aneurysms beyond that explained by aneurysm diameter. Fuller evidence on which to base surveillance intervals for patients in screening programmes requires a meta-analysis based on individual patient data.

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Introduction

Four population-based trials of screening for abdominal aortic aneurysm (AAA)^{1–4} have been summarized in both a best-evidence systematic review⁵ and a Cochrane review⁶. These trials showed that, for men, screening reduces the incidence of aneurysm rupture and hence aneurysm-related mortality. The Cochrane review reported that, for aneurysm-related mortality, screening conferred a benefit with an odds ratio of 0.60 (95 per cent confidence interval (c.i.) 0.42 to 0.68)⁶ and the systematic review⁵ reported a similar benefit with an odds ratio of 0.53 (0.47 to 0.78). These trials have provided the evidence in favour of population screening for older men. In the UK, a

national abdominal aortic aneurysm screening programme has been launched in England to detect AAA in men aged 65 years and monitor small aneurysms (3.0–5.5 cm in diameter). However, this and similar programmes in other countries would benefit from evidence-based policies for their surveillance protocols. Such policies will depend, in large part, on the growth rate and rupture rate of aneurysms.

Apart from the screening trials, a number of other observational studies have reported on growth rates of small aneurysms and recommended different frequencies of follow-up examinations. In many cases, simple linear regression has been used to estimate growth rates^{7–9}. This

does not take into account that aneurysm growth rate may accelerate with increasing diameter¹⁰. In addition, it has been reported that aneurysm growth is faster in smokers and slower in patients with diabetes, whereas differences between the sexes are still unclear^{10–12}. Some trials also have used either antibiotics or beta-blockers in an attempt to reduce AAA growth^{9,13}. Although none of these trials provided persuasive evidence that any treatment slows small aneurysm growth, these studies still provide data on aneurysm growth rates.

The aim of this study was to synthesize the published data on growth rates for small aneurysms in a systematic review.

Methods

The systematic review followed quality reporting guidelines set by the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA)¹⁴. MEDLINE, Embase on Ovid SP, CENTRAL Issue 4, 2009, ClinicalTrials.gov, and controlled-trials.com were searched up until the end of 2009 using search strategies shown in *Appendix S1* (supporting information). No filters were used to restrict study designs, nor were there any language restrictions. In addition, reference lists were searched for further studies to be included.

Eligibility criteria and study selection

Two authors independently reviewed potential studies according to a set of eligibility criteria. The study participants (minimum 50, men or women; at least 50 years of age) must have had a small infrarenal AAA, with a baseline diameter of between 3.0 and less than 5.5 cm (anteroposterior or transverse) assessed by either serial ultrasonography or computed tomography (CT) on at least two occasions separated by at least 6 months. Studies that included wider diameter ranges were used provided that growth rate estimates were available separately with the range 3.0–5.5 cm. At this stage, to enable reading in-house, languages were restricted to English, Spanish, French, Swedish, Danish and Norwegian. In addition, the following were excluded: review articles, studies in which patient data were duplicated (in which case the most recent or comprehensive study was used), non-human studies, editorials, letters, case reports, studies containing patients previously treated by AAA surgery or aneurysms of other arteries, and studies reporting on patients with Marfan syndrome. Study authors were contacted for further information if aneurysms could not easily be separated according to size range.

Data collection

A data extraction form to identify variables and potential biases in the eligible studies was designed. In particular, the following were identified: study design (prospective, retrospective, randomized, multicentre), source of patients (population screening, hospital screening), defined intervention policy, method and frequency of follow-up (ultrasonography, CT), patient recruitment (number of patients having 2 or more scans, excluded patients), presence of a mortality review committee, duration of follow-up (mean, median, standard deviation), inclusion criteria, recruitment period, trial using a particular drug, baseline data including age, sex, ethnicity and other cardiovascular risk factors (such as blood pressure, smoking status, drugs, ischaemic heart disease, peripheral arterial disease, diabetes), outcomes (how aortic diameter was measured, measurement variability, if growth was reported by size band, number of non-AAA deaths, number of AAA repairs, who carried out the aortic measurements), analysis (statistical methods used), author affiliation, date of publication and country (where study was undertaken). The same two authors independently extracted data from the potentially eligible primary studies and cross-checked their results. Any disagreements between the two reviewers were settled by a third person.

Any studies that failed to provide essential variables (growth rates, frequency and duration of follow-up) were either rejected, or the study authors were contacted for missing information. If study authors did not respond to the reviewers' repeated correspondence, these studies were withdrawn from the selected shortlist of publications. In addition, reasons for exclusion of particular studies were given.

Estimation of aneurysm growth rate

The reported overall mean growth rate (millimetres per year) together with its standard error was extracted from each study, together with mean growth rates reported in size bands. Median growth rates were used if means were not reported (3 of 15 studies). If percentage changes in AAA size were reported, these were converted to mean growth rates by using the midpoint of the reported size band.

Where 95 per cent c.i. were quoted in place of standard errors, these were converted by assuming normality and using the formula $\text{s.e.m.} = (\text{ucl} - \text{lcl})/3.92$, where ucl and lcl are the upper and lower limits of the 95 per cent c.i. If a sample standard deviation and number of subjects was quoted then this was converted to a standard error of the mean using the formula $\text{s.e.m.} = \text{s.d.}/\sqrt{n}$, where n is the

number of subjects. If a 95 per cent reference range was quoted, this was first converted to a standard deviation using the formula $s.d. = (urr - lrr)/3.92$, where urr and lrr were the upper and lower limits of the 95 per cent reference range, and then to a standard error of the mean, as above. Similarly, reported interquartile range (i.q.r.) values were first converted to standard deviations using the formula $s.d. = i.q.r./1.35$.

Meta-analysis

Studies that reported a number of different growth rates by size band (within the 3.0–5.5-cm range) but no overall growth rate were subjected to their own mini meta-analysis in which the size band estimates were pooled (using a fixed-effect meta-analysis) to obtain an additional overall growth rate estimate for that study. Studies with estimates from two treatment arms^{9,13} were also pooled in this way to obtain an overall study estimate. The overall estimates (one for each study) were then combined in a conventional random-effects meta-analysis.

Separate meta-analyses were conducted for growth rates reported in 5-mm size bands in an attempt to account for some of the heterogeneity between study estimates. To account more comprehensively for heterogeneity resulting from varying AAA diameter ranges, a meta-regression model was fitted to the data using average AAA diameter as an explanatory variable. Size band-specific estimates were included by using the midpoint of the size band as a proxy for average AAA diameter. Studies with only an overall estimate were included by using the mean baseline aneurysm diameter as the co-variable value. A three-level model was then used to account for heterogeneity between studies, and between size bands within a study, after adjusting for average AAA diameter¹⁵. Mean age and proportion of women in each study were also investigated as explanatory variables.

All analyses were conducted using Stata® version 11 (StataCorp, College Station, Texas, USA) and Spotfire S+® 8.1 (Tibco Software, Palo Alto, California, USA).

Results

Identification of relevant studies

A total of 10 160 study titles were identified by the initial search strategy and, of these, 9951 were excluded after title searching (*Fig. 1*). A total of 209 potential papers were selected, of which two had been identified by searching reference lists. In the next stage, abstracts were reviewed and 61 papers were selected for further review of full-text publications. Of the eligible full-text publications, 46

were excluded for one or more of the following reasons: language (2), duplicated data/patients (12), no original data/data synthesis only (2), growth rates not available/no longitudinal study (11), selection criteria unspecified (1), patient selection bias (8), incorrect aneurysm size range (13), no defined intervention (2), too few patients (6), growth rates not according to size range (2), not restricted to AAA (1), no frequency of follow-up (2) and retrospective intervention policy (1). A full list of excluded studies, with reasons, is provided in *Table S1* (supporting information). Fifteen studies were identified as potentially eligible for inclusion in the systematic review (*Table 1*)^{7–13,16–23}.

Study characteristics

The publication dates of the 15 potentially eligible studies ranged from 1994 to 2009, with patient recruitment from 1976 to 2005. Of these, 12 were prospective studies (including 3 randomized trials); the two with earliest start dates were mainly prospective but probably retrospective for the earliest phase^{16,20}, and one study reported retrospective data⁷. Aneurysm growth was the

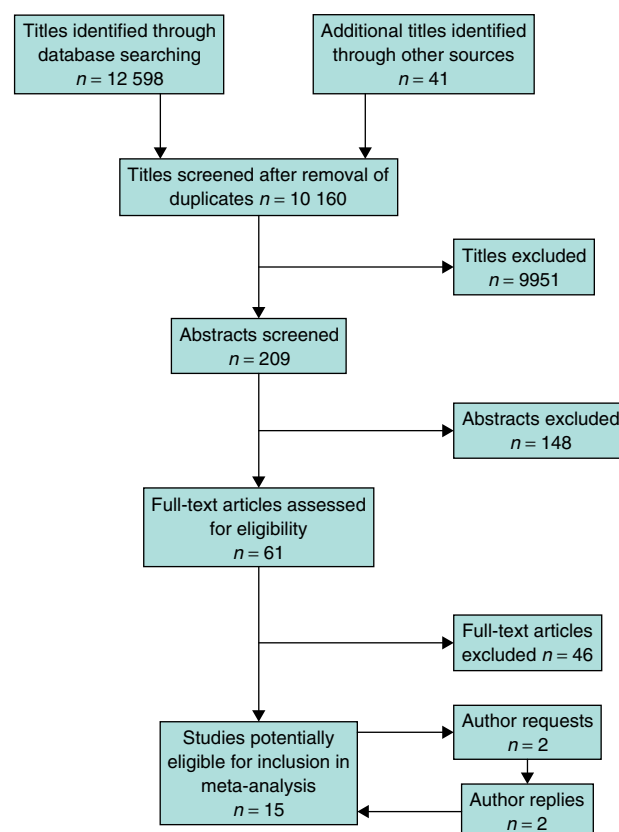


Fig. 1 PRISMA flow diagram

Table 1 Published growth rates of small abdominal aortic aneurysms (initial diameter 3.0–5.5 cm)

Reference	Country and enrolment dates	No. of patients (women)	Mean baseline aortic diameter (mm)	Imaging	Frequency of follow-up (intervention threshold)	Duration of follow-up	Method of growth rate estimation (values reported)	Baseline AAA size range (mm)	Mean (s.e.m.) growth rate (mm/year)
Brady <i>et al.</i> ¹⁰ 2004	UK 1991–1995	1743 (387)	43; maximum external AP	US	3 months if ≥ 50 mm; 6 months if < 50 mm (5.5 cm)	3312 patient-years	Hierarchical models: linear, quadratic (mean)	28–85 ($n = 1743$) 40–45 ($n = 518$)	2.6(0.03) 2.7(0.06)
Brown <i>et al.</i> ¹⁶ 2003	Canada 1976–2001	895 (207)	40; dimension NR	US (1976–1982); CT (1983 onwards)	6 months	3088 patient-years	NR (mean)	30–49 ($n = 895$) 30–34 ($n = 191$) 35–39 ($n = 204$) 40–44 ($n = 306$) 45–49 ($n = 194$)	3.8(0.2) 2.8(0.3) 3.4(0.3) 4.5(0.3) 5.2(0.4)
Karlsson <i>et al.</i> ⁹ 2009	Sweden 2002–2005	211 (50)	40 in both groups; wider of external AP and transverse	US	6 months	18–36 months	Linear regression (median)	35–49 ($n = 211$)	2.2(0.1)
Lederle <i>et al.</i> ¹⁷ 2002	USA 1992–1996	567 (2)	47; external cross-section in any plane	US; CT (baseline and ≥ 53 mm)	6 months (5.5 cm)	Mean 3.0 years	(Last – first diameter)/time (median)	40–54 ($n = 567$)	3.2(0.08)
Lindholt <i>et al.</i> ¹⁸ 2000	Denmark 1994–1998	151 (0)	NR; external AP	US	12 months (5.0 cm)	1–5 years	(Last – first diameter)/time (mean)	30–49 ($n = 151$)	2.8(0.20)
McCarthy <i>et al.</i> ⁸ 2003	UK 1990–2002	496 (0)	34; AP, external A to internal P	US	12 months if 26–39 mm; 6 months if > 40 mm (5.5 cm)	Mean(s.d.) 4.2(2.4) years	(Last – first diameter)/time (median)	30–39 ($n = 496$)	1.9(0.1)
Propranolol Aneurysm Trial Investigators ¹³ 2002	Canada 1993–1998	548 (87)	38 in both groups; external AP	US	6 months (5.0 or 5.5 cm by centre)	Mean(s.d.) 2.5(1.1) (range 0–4.5) years	Unclear: growth per year (slope) (mean)	30–50 ($n = 531$)	2.4(0.1)
Santilli <i>et al.</i> ¹⁹	USA 1990–1996	790 (0)	33; wider of external AP and lateral	US	Unclear (5.5 cm)	3071 patient-years	NR (mean)	30–39 ($n = 790$) 30–34 ($n = 578$) 35–39 ($n = 212$)	1.6(0.07) 1.5(0.08) 2.0(0.13)
Schewe <i>et al.</i> ²⁰ 1994	Germany 1976–1993	134 (NR)	37; mean of AP and transverse	US	6 months	536 patient-years	(Last – first diameter)/time (mean)	30–39 ($n = 69$) 40–49 ($n = 30$) > 50 ($n = 11$)	2.3(–) 3.1(–) 3.9(–)
Schlösser <i>et al.</i> ²¹ 2008	The Netherlands 1996–2005	147 (16)	39; AP diameter	US	12 months if 30–39 mm; 6 months if 40–55 mm (5.5 cm)	Median 3.3 (range 0.5–11.1) years; 599 patient-years	Linear regression (mean)	30–55 ($n = 147$)	2.5(0.26)
Schouten <i>et al.</i> ⁷ 2006	The Netherlands 2002–2005	150 (24)	38; maximum external AP	US	6–12 months (5.5 cm)	Median 3.1 years	Linear regression (mean)	25–53 ($n = 150$)	2.95(0.23)

Table 1 (Continued)

Reference	Country and enrolment dates	No. of patients (women)	Mean baseline aortic diameter (mm)	Imaging	Frequency of follow-up (intervention threshold)	Duration of follow-up	Method of growth rate estimation (values reported)	Baseline AAA size range (mm)	Mean (s.e.m.) growth rate (mm/year)
Solberg <i>et al.</i> ¹² 2005	Norway 1994–1995	234 (49)	35; external transverse or AP	US	3 or 6 months	1212 patient-years	Linear regression (mean)	30 to > 49 (n = 234) 30–34 (n = 87) 35–39 (n = 58) 40–44 (n = 23) 45–49 (n = 11) > 49 (n = 9)	1.82(0.14) 1.80(0.25) 1.75(0.14) 2.31(0.48) 3.36(0.95) 2.63(1.57)
Vardulaki <i>et al.</i> ²² 1998	UK Chichester 1983–?	519 men + women	NR; wider of AP and transverse measurements	US	3–12 months (6.0 cm initially)	Mean 3.4 years	Hierarchical models (% change in growth rates)	30 to ≥ 50 (n = 519) 30–39 40–49 ≥ 50	0.9(0.1) 0.7(0.2) 1.5(0.4) 3.5(0.7)
Vardulaki <i>et al.</i> ²² 1998	UK Huntingdon 1991–1996	498 (0)	NR; external AP	US	3–12 Months (4.5 cm)	Mean 2.3 years	Hierarchical models (% change in growth rates)	30–49 (n = 498) 30–39 40–49	–0.3(0.2) –0.6(0.3) 0.9(0.6)
Vega de Céniga <i>et al.</i> ^{11,†} 2006	Spain 1988–2004	352 (19)	36; wider of external AP and transverse	US if 30–39 mm; CT if 40–49 mm	12 months if 30–39 mm; 6 months if 40–49 mm (5.0 cm)	Overall mean(s.d.) 55.2(37.4) (range 6.3–200) months	(Last – first diameter)/time (mean)	30–49 (n = 352)	2.87(0.23)
Vega de Céniga <i>et al.</i> ²³ 2008	Spain 1998–2004	195 (12)	42.5; wider of maximum external AP or transverse	CT	6 months (5.0 cm)	Mean(s.d.) 50.0(36.4) (range 6.5–194) months	(Last – first diameter)/time (mean)	40–49 (n = 195)	3.95(0.43)

Values shown in italics have been calculated subsequently from the published data using the methods described in the text. †Patient group extended in Vega de Céniga *et al.* (2008)²³. AP anterior–posterior; US, ultrasonography; NR, not reported; CT computed tomography.

primary outcome measure in ten studies. Overall, there were 7630 people included in these 15 studies (although the two Spanish studies may have included some duplicated patients^{11,23}). Some studies did not report accurately on the sex of participants^{20,22}, but in those that did the proportion of women ranged from 0 to 24 per cent of the study population. The mean baseline age ranged from 65 to 71 years, although age was not reported in two studies^{16,20}. The study size ranged from 134 to 1743 patients with most patients followed up for between 1 and 5 years; not all of these studies stated the mean length of follow-up or patient-years of follow-up.

Most studies used ultrasonography to monitor aortic diameter, but the plane and cursor positioning (internal *versus* external) varied between the studies and the precise plane of reference was not specified for some studies. Some studies used CT as well as ultrasonography^{16,17,23}. Most of these studies included aortic diameters from 30 mm (at baseline), except three that reported from either 25 mm^{7,18}

or 28 mm¹⁰. Not all studies restricted their reporting to the aneurysm diameter range of interest (3.0–5.5 cm), and in some instances substudies were identified that reported on a more restricted range^{10,16,23}. Different methods were used to estimate aneurysm growth, usually reported as millimetres per year, with linear regression or (last – first diameter)/time being the most common; two studies did not report how they estimated aneurysm growth^{16,19}. One study reported only percentage changes in aneurysm diameter and used data from two screening programmes (Chichester and Huntingdon)²². Some studies were more than 10 years old, so that some requests to authors for further information met with little success^{16,20,22}. These and other details of the included studies are shown in Table 1. Quality indicators for both imaging and design of the 15 included studies are listed in Table S2 (supporting information).

Other patient characteristics, such as ethnicity, history of smoking, prevalence of diabetes, blood pressure,

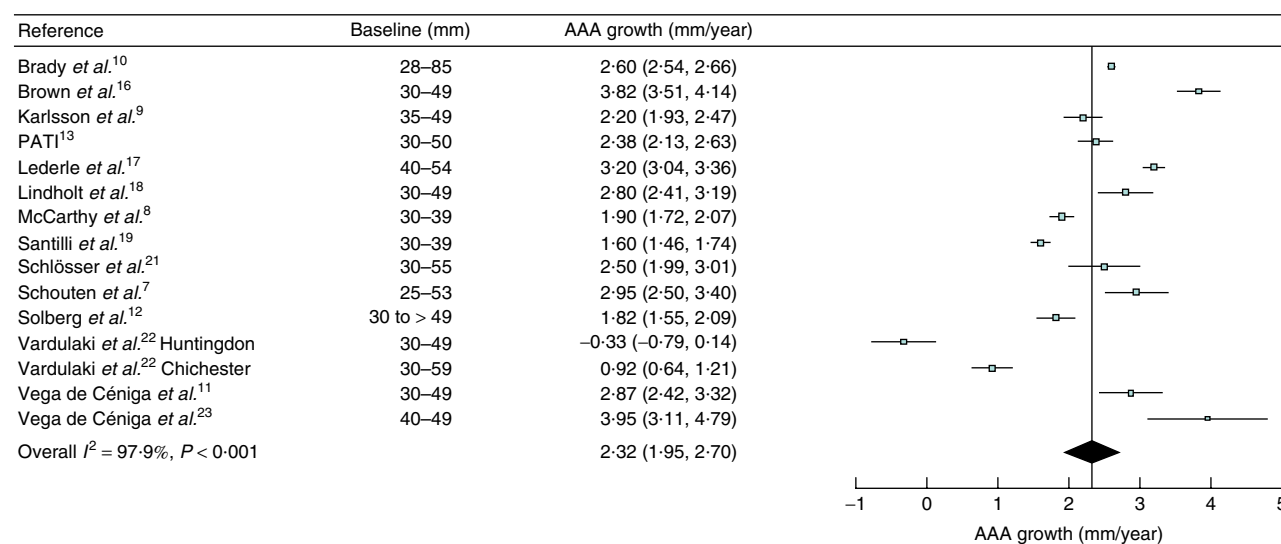


Fig. 2 Overall abdominal aortic aneurysm (AAA) growth rate estimate for each study, with baseline AAA diameter size range. Estimates were pooled using a random-effects model, owing to considerable heterogeneity ($I^2 = 97.9$ per cent). An estimate from Schewe and colleagues²⁰ could not be included as no standard error was available. AAA growth rates are shown with 95 per cent confidence intervals. PATI, Propranolol Aneurysm Trial Investigators

proportion of people with ischaemic heart disease and peripheral arterial disease, were reported variably across the 15 studies.

Comparison of small aneurysm growth rates

Overall mean growth rate estimates are shown in Fig. 2, with separate estimates for the Huntingdon and Chichester studies reported by Vardulaki and colleagues²². There was very substantial heterogeneity between study estimates ($I^2 = 97.9$ per cent), with reported growth rates ranging from -0.33 to $+3.95$ mm/year. The Huntingdon study²² was reported as having a negative growth rate and the largest growth rate was reported from a study that only included 40–49-mm diameter aneurysms²³. One study could not be included because no standard error could be calculated from the information reported²⁰. The random-effects meta-analysis estimate of the mean aneurysm growth rate was 2.32 (95 per cent c.i. 1.95 to 2.70) mm/year. Restriction of the meta-analysis to studies that used only ultrasonography after 1990 (reflecting potentially better imaging quality), reduced the overall growth rate slightly to 2.05 (1.64 to 2.45) mm/year although the heterogeneity remained high ($I^2 = 97.5$ per cent).

For studies that reported mean growth rates by 5-mm diameter bands^{8,11,12,16,18,19}, the rates are summarized in Fig. 3. Estimates within these size bands were generally

more homogeneous than the overall estimates, although heterogeneity still remained (I^2 ranged from 11.2 to 91.0 per cent). Growth rates increased steadily with aneurysm diameter band, with a pooled mean growth rate of 1.81 (1.55 to 2.07) mm/year for individuals whose baseline AAA diameter measured 3.0 – 3.4 cm compared with 4.96 (4.25 to 5.66) mm/year for those whose baseline diameter measured 4.5 – 4.9 cm. The greater number of patients in the smaller-diameter bands is one reason why the widths of the 95 per cent c.i. increase with aneurysm diameter.

The statistical method used to calculate growth rates and the study design (retrospective or prospective) were associated significantly with growth rates. Studies that used hierarchical modelling or linear regression had mean(s.e.m.) growth rates that were respectively $1.52(0.51)$ and $0.40(0.40)$ mm/year smaller than those of studies that used (last – first diameter)/time to report growth rate. Prospective studies had mean growth rates that were $1.11(0.39)$ mm/year smaller than those of either retrospective or partially retrospective designs, although this effect was no longer significant after adjustment for the method used to calculate growth rate.

A meta-regression with average aneurysm diameter as an explanatory variable resulted in a strong trend between diameter and growth rate (Fig. 4). After adjusting for average diameter, between-study heterogeneity was estimated to be about twice that of heterogeneity between

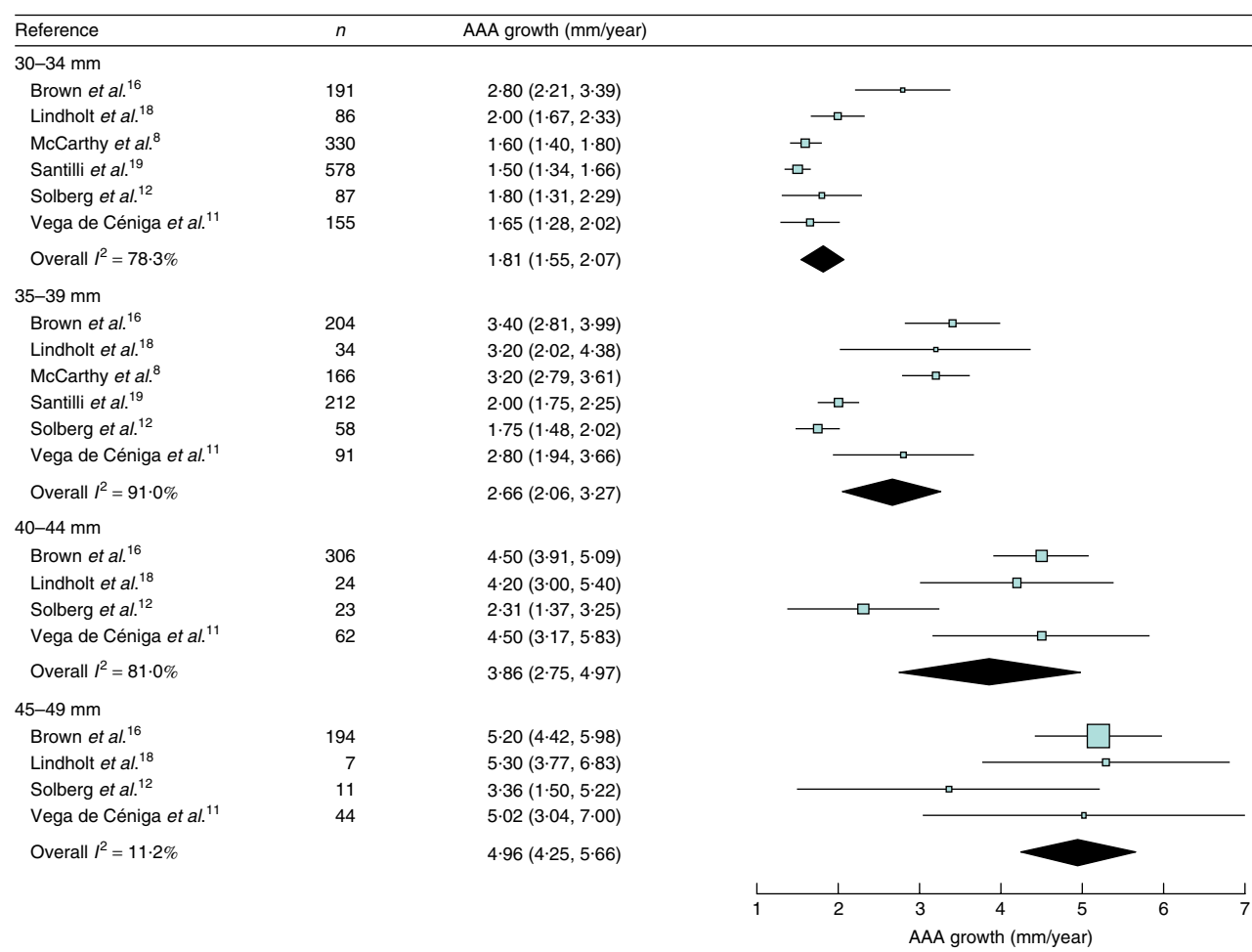


Fig. 3 Abdominal aortic aneurysm (AAA) growth rate by 5-mm size ranges of baseline aneurysm diameter. Estimates in each subgroup were pooled in random-effects models. AAA growth rates are shown with 95 per cent confidence intervals

estimates within a study. A 10-mm increase in AAA diameter was found to be associated with a mean(s.e.m.) 1.62(0.20) mm/year increase in growth rate. The age and sex of included patients were available for nearly all studies. They were assessed as explanatory variables but found to be not statistically significant; a 10 per cent increase in the proportion of women in a study increased the mean growth rate by a modest 0.13(0.26) mm/year, whereas a 5-year increase in mean study participant age decreased the growth rate by 0.01(0.56) mm/year.

Based on the linear relationship between growth rate and aneurysm diameter (Fig. 4), the size of aneurysms is expected to grow exponentially with time. Given the meta-regression relationship shown, aneurysms with diameters of 3.0, 3.5, 4.0, 4.5 and 5.0 cm would be expected, on average, to take 9.6, 6.2, 4.0, 2.3 and 1.1 years respectively to reach 5.5 cm.

Discussion

Evidence in favour of surveillance rather than intervention (either open surgery or endovascular repair) for small AAA (3.0–5.5 cm in diameter) has come from four randomized trials^{17,24–26}. The interval between surveillance scans for such small aneurysms is not underpinned by strong evidence. This is the first systematic review of small aneurysm growth rates since their inclusion in the earlier review of surgical management of aneurysms from Hallin *et al.*²⁷, which covered the literature from 1990 to 1997. Unlike this earlier review that included only 816 patients from 13 different studies, the eligibility criteria for studies (50 or more patients) were not relaxed in the present review, which allowed the identification of 15 suitable studies with 7630 people for inclusion in a meta-analysis. Many of these

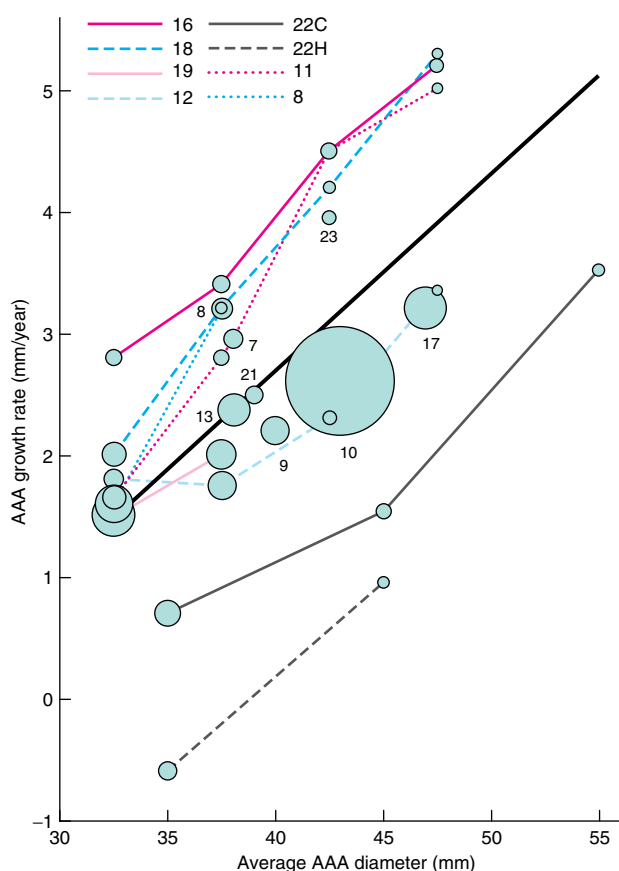


Fig. 4 Meta-regression of abdominal aortic aneurysm (AAA) growth rate estimates by AAA diameter. The overall regression line is shown by the solid bold line. The midpoint of the reported size range was used to calculate AAA diameter for range-specific estimates, whereas the mean baseline diameter was used for overall estimates. Estimates from the same study are linked. Circle areas are in proportion to the amount of information (inverse variance of the estimate). C, Chichester; H, Huntingdon

7630 patients came from randomized trials investigating the management of aneurysms^{9,10,13,17,22} or population-based screening studies^{8,12,19}. The pooled mean growth rate for small aneurysms (3.0–5.5 cm in diameter) of 2.32 (1.95 to 2.70) mm/year should be viewed with caution. Although the c.i. on this estimate were acceptable, given the reproducibility of either ultrasonographic or CT diameters, the heterogeneity was very high, even beyond that explained by aneurysm diameter range.

There are many explanations for the large heterogeneity, particularly methodological and patient population issues. The methodological issues include that patients had been entered into these studies since 1976, a 35-year time window during which the quality of aortic imaging has improved dramatically. Second, some recent studies

used imaging modalities other than ultrasonography, such as CT, and it is known that there is poor agreement between CT and ultrasonographic aortic diameter measurements^{28,29}. Some studies used both methods of imaging^{11,16,17}. However, a sensitivity analysis of studies that used only ultrasonographic imaging after 1990 showed that this was not associated with a reduction in heterogeneity. Third, aortic diameter has been measured in a variety of different planes, and measurement cursors have been positioned on both the external and internal walls of the aorta. In addition, only a minority of studies specified the standardization of imaging protocol between observers (Table S2, supporting information). Fourth, growth rates have been estimated in a variety of different ways using (last – first diameter)/time, linear regression or complex or multilevel modelling, and it has been reported that linear regression can overestimate aneurysm growth by up to 40 per cent compared with multilevel modelling¹⁰. Hierarchical modelling also resolves the problem of a small number of measurements possibly leading to exaggerated growth rates¹⁰. There was evidence that some of the heterogeneity is explained by the use of linear regression and in particular (last – first diameter)/time to report aneurysm growth rates.

The patient population issues include ethnicity (which was reported rarely), the intervention policy of each study, which varied from aneurysm repair at 4.5 cm in the Huntingdon study to 6 cm in the Chichester study²², the variable proportion of women in each study, which ranged from 0 to 24 per cent, and whether the aneurysm was identified by population screening or in hospital. During the period of recruitment to these studies, 1976–2005, there have been important improvements in medical therapy, with some studies reporting that use of statins slows the growth of aneurysms, whereas angiotensin converting enzyme inhibitors may increase the growth of small aneurysms^{7,30}. Medical therapies, smoking and co-morbidities were reported inconsistently across the 15 studies included in the present review and so their influence on growth rates was not evaluated here. However, growth rates in the best medicated patient group²¹ were not obviously lower than those in the other studies. Similarly, there were no significant effects of either mean baseline patient age or the percentage of women in a study on aneurysm growth, even though some previous studies have suggested that aneurysms grow faster in women¹².

Although this meta-analysis based on the published literature provides very strong evidence that growth rates increase markedly with aneurysm size, it provides only partial information about appropriate surveillance intervals for small aneurysms. From the meta-regression,

the growth rate for a 3.5-cm aneurysm is estimated at 1.90 mm/year, whereas that for a 4.5-cm aneurysm is 3.52 mm/year, both rates being somewhat lower than those presented in the earlier review²⁷. Given an exponentially increasing aneurysm diameter, as implied from the meta-regression in Fig. 4, it would take on average 6.2 years for a 3.5-cm aneurysm to grow to 5.5 cm, whereas a 4.5-cm aneurysm would take only 2.3 years. So surveillance intervals for a 4.5-cm aneurysm should be of the order of one-third of those for a 3.5-cm aneurysm. However, the meta-regression does not provide information about the variability of growth rates between individuals.

The variability of growth rates both between individuals and over time is known to be substantial, with some aneurysms growing relatively quickly and others growing slowly or not at all, and some growing erratically. The conclusions in this review are based on data from both men and women, whereas most population screening programmes are restricted to men. Therefore, study of individual patient data from longitudinal studies of aneurysm growth is required as this would provide the scope to investigate the influence of patient characteristics (including age, sex, smoking, diabetes and other relevant factors) on growth rates, to provide predictions (with uncertainty intervals) of future aneurysm size for individuals. Then analysis would allow choice of appropriate surveillance intervals so that the probability of exceeding 5.5 cm before the next follow-up is kept below a specified threshold, such as 5 per cent, 2 per cent or less. In addition, the frequency of surveillance needs to be evaluated in terms of its operational feasibility, patient acceptability and economic consequences.

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Supporting information

Additional supporting information may be found in the online version of this article:

Appendix S1 Search strategy (Word document)

Table S1 Studies excluded from systematic review with reasons (Word document)

Table S2 Quality assessment of studies included in the systematic review (Word document)

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