

ORIGINAL ARTICLE

Growth of Screen-Detected Abdominal Aortic Aneurysms in Men: A Bayesian Analysis

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There is considerable interindividual variability in the growth of abdominal aortic aneurysms (AAAs), but an individual's growth observations, risk factors, and biomarkers could potentially be used to tailor surveillance. To assess the potential for tailoring surveillance, this study determined the accuracy of individualized predictions of AAA size at the next surveillance observation. A hierarchical Bayesian model was fitted to a total of 1,732 serial ultrasound measurements from 299 men in whom ultrasound screening identified an AAA. The data were best described by a nonlinear model with a constant first derivative of the AAA growth rate with size. The area under the receiver operating characteristic (ROC) curves for predicting whether an AAA was ≥ 40 or ≥ 50 mm at the next observation were 0.922 and 0.979, respectively, and the median root mean squared error was 2.52 mm. These values were nearly identical for models with or without plasma D-dimer effects.

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The abdominal aorta is considered aneurysmal if its greatest diameter is at least 30 mm. Abdominal aortic aneurysms (AAAs) most commonly affect older men, with a prevalence rate of ~2–8% in men older than 65 years.^{1–3} The primary risk associated with AAA is aortic rupture, which is estimated to be fatal in 68–90% of cases.^{4,5} AAAs are generally asymptomatic until rupture occurs and are mostly diagnosed on ultrasound or computed tomography scanning used for evaluation of other medical conditions or during population screening studies.^{6–9} Because AAA rupture risk increases with AAA diameter,^{10–12} surgical repair is generally recommended for AAAs measuring 50–55 mm or more depending on local guidelines, whereas smaller AAAs are treated conservatively followed by repeat imaging, usually using ultrasound.

There is considerable inter- and inpatient variability in the growth rate of AAAs with some AAAs expanding rapidly while others grow slowly or remain stable.^{13–15} Therefore, regular surveillance of AAAs is recommended to monitor expansion. This surveillance strategy could be tailored if the growth rate of individual patients was more precisely known while accounting for within-individual variability; surveillance could be less frequent for AAAs unlikely to reach 50 mm for several years and more frequent for those likely to reach 50 mm rapidly. One approach for estimating the growth rate of an individual AAA is to include existing observations collected during surveillance of that AAA to estimate its growth rate. In other words, the growth rate of an individual AAA is initially set to the population average estimate, adjusting for covariate effects, and is adjusted further after each of its subsequent size measurements. The objective of this work was to first develop a hierarchical, Bayesian model that describes growth of small AAA in men and then use this model to individualize AAA growth rate in each individual by updating the model prediction after each observation. The aim was to determine the accuracy of

AAA size predictions at the next observation compared with the actual measurements.

Other risk factors, biomarkers, or measures that more precisely predict AAA growth may be of clinical value.¹⁶ One example is plasma D-dimer, a factor that has been previously associated with AAA growth using regression models.¹⁷ Although plasma D-dimer is associated with the population trend in AAA growth, the effect of plasma D-dimer (or other potential biomarkers) on individual AAA size predictions that are adjusted as additional surveillance size measurements is unknown. Therefore, we also assessed the added value of patient characteristics collected from blood tests, including plasma D-dimer, in predicting AAA size observations.

RESULTS

A total of 875 men were diagnosed with a small AAA (30–49 mm) during the Western Australia screening study. Of these, 299 had both serial AAA diameter measurements and a D-dimer measurement and were included in this study cohort. In these men, the median AAA diameter at screening was 32.7 mm (interquartile range of 30.8–36.0 mm). The men were followed up for a median of 5.5 years (interquartile range of 5–6 years) and underwent a total of 1,732 AAA size measurements with a median of six (interquartile range of 6–7) measurements per patient. The median plasma D-dimer concentration for patients was 326 ng/ml (interquartile range of 143–786 ng/ml). The demographic characteristics, risk factors at screening, and blood biochemistry of these men are listed in **Table 1**.

AAA growth model

The serial AAA size measurements of individual men were best described by the AAA growth model with a constant first

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Table 1 Characteristics of the men included in this study

Characteristic	Value
Number of men	299
AAA diameter at baseline, median (q1, q3)	32.7 mm (30.8, 36.0)
Duration of follow-up, median (q1, q3)	5.5 years (5, 6)
AAA measurements per patient, median (q1, q3)	6 (6, 7)
Demographic characteristics	
Age, median (q1, q3)	72 years (69, 75)
Body mass index, median (q1, q3)	27.2 (25.1, 29.6)
Waist-to-hip ratio, median (q1, q3)	0.97 (0.93, 1.01)
Systolic blood pressure, median (q1, q3)	155 mm Hg (142, 169)
Diastolic blood pressure, median (q1, q3)	91 mm Hg (83, 135)
Medical conditions at baseline	
Diabetes, <i>N</i> (%)	42 (14%)
Hypertension, <i>N</i> (%)	147 (49%)
Coronary heart disease, <i>N</i> (%)	113 (38%)
Smoking history, <i>N</i> (%)	252 (84%)
Most cigarettes per day, median (q1, q3)	19 (7, 30)
Pack year history, median (q1, q3)	29 (8, 55)
Blood measurements	
D-dimer protein, median (q1, q3)	326 ng/ml (142, 785)
Glucose, median (q1, q3)	5.3 mmol/l (4.9, 5.9)
Creatinine, median (q1, q3)	92 μmol/l (80, 111)
Cholesterol, median (q1, q3)	4.6 mmol/l (4.0, 5.3)
Triglycerides, median (q1, q3)	1.2 mmol/l (0.9, 1.7)
High-density lipoprotein, median (q1, q3)	1.2 mmol/l (1.1, 1.5)
Low-density lipoprotein, median (q1, q3)	3 mmol/l (2, 3)
Homocysteine, median (q1, q3)	13.9 μmol/l (11.2, 17.7)
C-reactive protein, median (q1, q3)	2.45 mg/l (1.40, 5.06)

AAA, abdominal aortic aneurysm.

derivative of AAA growth rate with size (Table 2). The mathematical representation of this model is presented in the Methods section, and examples of the population and individual fits to data are shown in Figure 1. In this model, the baseline size measurement was used to anchor the baseline size model parameter (10.0 mm per 10 mm increase; 95% credible interval (CrI), 9.95–10.01 mm). The baseline AAA growth rate model parameter was positively associated with both the baseline AAA size measurement (0.62 mm/year per 10 mm increase; 95% CrI, 0.27–1.04 mm/year) and the plasma D-dimer concentration (0.36 mm/year per decade increase; 95% CrI, 0.04–0.65 mm/year). The first derivative of the AAA growth rate with size model parameter was positively associated with both the baseline AAA size measurement (0.18/year per 10 mm increase; 95% CrI, 0.03–0.31/year per 10 mm) and the plasma D-dimer concentration (0.15/year per decade; 95% CrI, 0.05–0.25/year) but negatively associated with whether the patient was diabetic (−0.32/year for diabetics; 95% CrI, −0.45 to −0.18/year). In mathematical terms, the expected values of the parameters in the final model for the baseline AAA size $\bar{\beta}_{0,k}^{(i)}$, baseline AAA growth rate $\bar{\beta}_{1,k}^{(i)}$, and

Table 2 Deviance information criteria for model structures tested without covariate effects

Model	Deviance information criteria (Dbar, Dhat, pD)
Constant growth rate	7,113 (6,573; 6,032; 540)
Growth rate changes at a constant rate with time	6,630 (5,907; 5,185; 723)
Growth rate changes as a linear function of time with time	6,509 (5,664; 4,819; 845)
Growth rate changes as a linear function of size with time	Did not converge ^a
Growth rate changes at a constant rate with change in size	6,487 (5,938; 5,389; 549)

^aThe model did converge if, instead of a Wishart distribution, a series of inverse γ distributions were used as the prior distribution for parameter precisions. Using these prior distributions, the model with the growth rate that changes at a constant rate with change in size also had the lowest deviance information criteria (6,532).

constant first derivative of AAA growth rate with size $\bar{\beta}_{2,k}^{(i)}$ for the *k*th Markov chain Monte Carlo (MCMC) parameter set output from WinBUGS applied to the *i*th individual are (see Methods section for details on the mathematical model)

$$\bar{\beta}_{0,k}^{(i)} = \beta_{0,k}^{(Y(0))} \frac{Y_i(0)}{\text{median}(Y(0))}$$

$$\bar{\beta}_{1,k}^{(i)} = \beta_{1,k}^{(0)} + \beta_{1,k}^{(Y(0))} \frac{Y_i(0)}{\text{median}(Y(0))} + \beta_{1,k}^{(C^{(D-dimer)})} \frac{\log_{10}(C_i^{(D-dimer)})}{\text{median}(\log_{10}(C^{(D-dimer)}))}$$

$$\bar{\beta}_{2,k}^{(0)} = \beta_{2,k}^{(0)} + \beta_{2,k}^{(Y(0))} \frac{Y_i(0)}{\text{median}(Y(0))} + \beta_{2,k}^{(C^{(D-dimer)})} \frac{\log_{10}(C_i^{(D-dimer)})}{\text{median}(\log_{10}(C^{(D-dimer)}))} + \beta_{2,k}^{(Diabetes)} \text{Diabetes}_i$$

where $Y_i(0)$, $C_i^{(D-dimer)}$, and Diabetes_i are the baseline AAA size measurement, plasma D-dimer concentration, and diabetes status for the *i*th man, respectively. The parameter values for the final model are given in Table 3.

In a sensitivity analysis using categorized plasma D-dimer concentrations, there were significant differences in the baseline growth rate model parameter for patients with >900 ng/ml vs. those with ≤150 ng/ml and in the first derivative of the AAA growth rate with size model parameter for the groups with >900 and 301–900 ng/ml vs. those with ≤150 ng/ml. The deviance information criteria value for the model using categorized plasma D-dimer concentrations was nearly identical to the model using log-transformed continuous plasma D-dimer measurements (6,069 categorized vs. 6,070 continuous plasma D-dimer).

Accuracy of AAA size predictions

A total of 1,677 size measurements of AAA had not been previously measured as ≥50 mm in size, and 27 men had an AAA that expanded to ≥50 mm during the study. The area

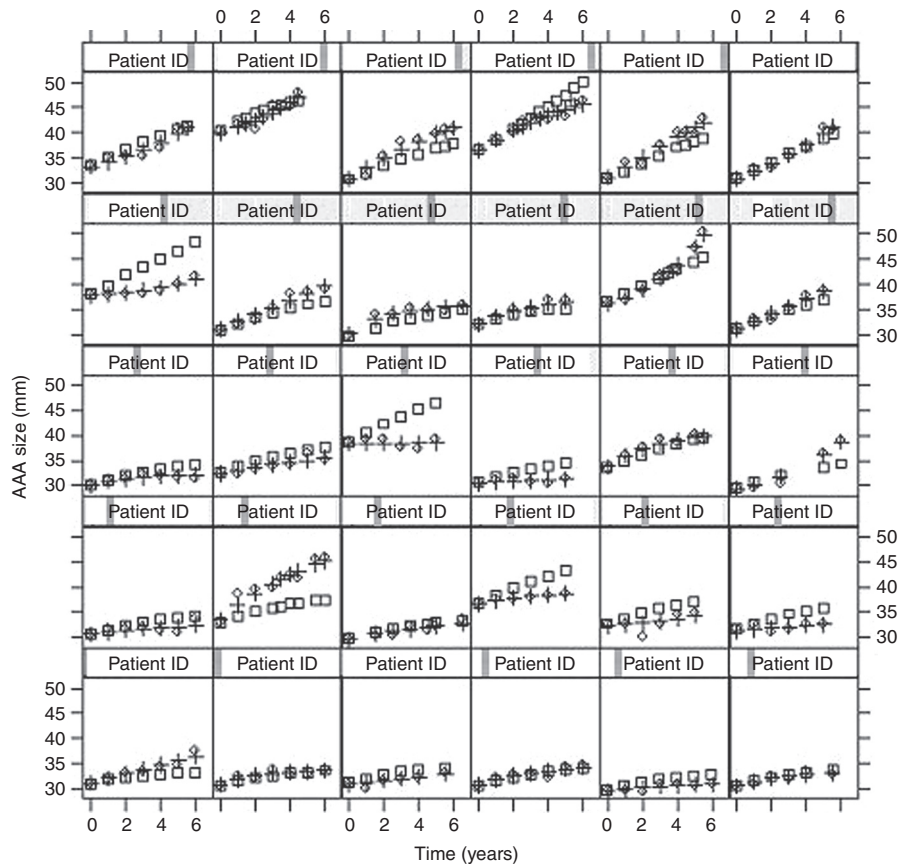


Figure 1 AAAs growth data (open circles), population predictions (open squares), and individual predictions for the final model (+) for every 10th patient by plasma D-dimer level. AAA, abdominal aortic aneurysm.

under the receiver operating characteristic (ROC) curve for predicting whether AAA would be ≥ 50 mm at the next size measurement was 0.979 for the final model (Figure 2a). Similarly, a total of 1,228 size measurements of AAA had not previously been measured as ≥ 40 mm in size, and 107 men had an AAA that expanded to ≥ 40 mm during the study. The area under the ROC curve for predicting whether AAA size would be ≥ 40 mm at the next size measurement was 0.929 for the final model (Figure 2b). For models without plasma D-dimer covariate effects, the area under the ROC curve for predicting whether an AAA would be ≥ 50 or ≥ 40 mm at the next size measurement were 0.979 and 0.922, respectively.

The median value of the root mean square error, RMSE, of final model predictions for the next follow-up AAA size measurement was 2.51 mm (90% CrI of median 2.510–2.514 mm). As shown in Table 4, the median RMSE of the final model predictions after a specific number of follow-up measurements ranged from 2.27 to 2.67 mm. The median RMSE of the model that did not include D-dimer covariate effects was 2.52 mm (90% CrI of median of 2.519–2.523 mm) and the values after a specific number of follow-up measurements ranged from 2.31 to 2.66 mm.

DISCUSSION

There is considerable inter- and intraindividual variability in the growth rate of small AAA, and surveillance of small AAA

is recommended until surgical intervention is warranted. The surveillance interval could potentially be tailored if the growth rate of a particular AAA was more precisely known. We identified an AAA growth model and found that the likelihood that an individual's AAA grows to ≥ 40 mm or ≥ 50 mm at the next surveillance measurement could be accurately predicted by adjusting the growth rate of an individual's AAA based on previous size measurements. In addition, the accuracy of the final model predictions for AAA size at the next surveillance measurement was virtually identical whether or not plasma D-dimer was included in the model.

Serial AAA size measurements were included in model predictions to make individual predictions and because these measurements are available clinically as patients undergo AAA surveillance. If only the baseline size measurement is available, a classification and regression tree analysis could be used to aid in the identification of patients with AAA that are likely to grow faster or slower based on the baseline size measurement and plasma D-dimer concentration as previously described.¹⁷ In this study, it was expected that the initial model prediction would be identical to those of the classification and regression tree analysis and adjusting growth predictions after each subsequent measurement would individualize the model predictions and reduce the predictive value of the plasma D-dimer covariate effect. We found that the predictive value of the plasma D-dimer concentration was negligible. However, a prospective study during which

Table 3 Median values (95% credible interval) of the final model's fixed parameters, covariance matrix, and residual variability

Fixed parameters	
$\beta_0^{\hat{Y}(0)}$ denotes covariate effect of baseline AAA size measurement on baseline AAA size model parameter	32.6 mm (32.5, 32.7)
$\beta_1^{(0)}$ denotes offset from covariate effects for baseline AAA growth rate model parameter	-1.61 mm/year (-3.08, -0.30)
$\beta_1^{\hat{Y}(0)}$ denotes covariate effect of baseline AAA size measurement on baseline AAA growth rate model parameter	2.03 mm/year (0.87, 3.40)
$\beta_1^{\hat{C}(\text{D-dimer})}$ denotes covariate effect of plasma D-dimer concentration on baseline AAA growth rate model parameter	0.90 mm/year (0.11, 1.64)
$\beta_2^{(0)}$ denotes offset from covariate effects for first derivative of AAA growth rate with size model parameter	-1.05/year (-1.52, -0.53)
$\beta_2^{\hat{Y}(0)}$ denotes covariate effect of baseline AAA size measurement on first derivative of AAA growth rate with size model parameter	0.59/year (0.11, 1.03)
$\beta_2^{\hat{C}(\text{D-dimer})}$ denotes covariate effect of plasma D-dimer concentration on first derivative of AAA growth rate with size model parameter	0.37/year (0.13, 0.62)
$\beta_2^{(\text{Diabetes})}$ denotes covariate effect of diabetes status on first derivative of AAA growth rate with size model parameter	-0.32/year (-0.45, -0.18)
Parameter covariance matrix	
$\sigma_{\beta_b}^2 = \sum_{1,1}$ denotes variance of baseline AAA size model parameter	0.19 mm ² (0.13, 0.28)
$\sigma_{\beta_a}^2 = \sum_{2,2}$ denotes variance of baseline AAA growth rate model parameter	1.11 mm ² /year ² (0.86, 1.42)
$\sigma_{\beta_b}^2 = \sum_{3,3}$ denotes variance of first derivative of AAA growth rate with size model parameter	0.10/year ² (0.07, 0.13)
$\sigma_{\beta_b, \beta_a}^2 = \sum_{1,2}$ denotes covariance between baseline AAA size and baseline AAA growth rate model parameters	0.30 mm ² /year (0.20, 0.41)
$\sigma_{\beta_b, \beta_b}^2 = \sum_{1,3}$ denotes covariance between baseline AAA size and first derivative of AAA growth rate with size model parameters	-0.06 mm/year (-0.09, -0.03)
$\sigma_{\beta_a, \beta_b}^2 = \sum_{2,3}$ denotes covariance between baseline AAA growth rate and first derivative of AAA growth rate with size model parameters	-0.15 mm/year ² (-0.22, -0.09)
SD of the residual variability	
σ_ε	0.97 mm (0.93, 1.00)

AAA, abdominal aortic aneurysm.

D-dimer is measured at the time of repeat imaging is needed to better estimate the predictive effect of D-dimer in a longitudinal model.

This model could potentially be used in the design of clinical trials for drugs that affect the growth of AAAs in men by simulating the likelihood of observing a significant change in AAA growth for a proposed trial protocol (e.g., number of patients needed, number and timing of observations per patients required, and duration of study). For example, we found a relatively low baseline growth rate to the measurement variability ratio (1.32 mm/year vs. 0.97 mm) and considerable interpatient variability in AAA growth rates. Qualitatively, this suggests that a clinical trial must have a sufficient duration and frequency of observation to separate the growth rate of individual subjects from the measurement noise and that a considerable number of patients may be needed to be enrolled to power the analysis. The model could also suggest subpopulations of patients more likely to have the desired AAA growth characteristics based on a patient's AAA size history, plasma D-dimer concentration, and diabetic status (assuming that the effects of the drug as a function of

AAA size, plasma D-dimer concentration, and diabetic status are known).

The dynamic AAA growth rate is consistent with the results from the UK Small Aneurysm Trial, which found that a quadratic model of growth rate with time best described their serial AAA size observation data.¹⁵ We found that a growth rate that changed as the size changed, rather than with time, better described the Health in Men Study (HIMS) data. This model has the advantage of directly incorporating the effects of AAA size on the growth rate. Previous analysis of the HIMS AAA growth data using regression methods found no evidence of nonlinear effects.¹⁷ This is likely because interindividual variability was not considered in the previous analysis. As shown in [Figure 2](#), there were clearly patients with positive, negative, as well as no curvature. Although the median value of the first derivative of the AAA growth rate with size model parameter is small at the population level (0.06/year), the relatively large interindividual variability on this parameter (0.32/year) suggests that there are individual patients with significant nonlinearity in the AAA growth trajectories. This implies that the substantial differences between

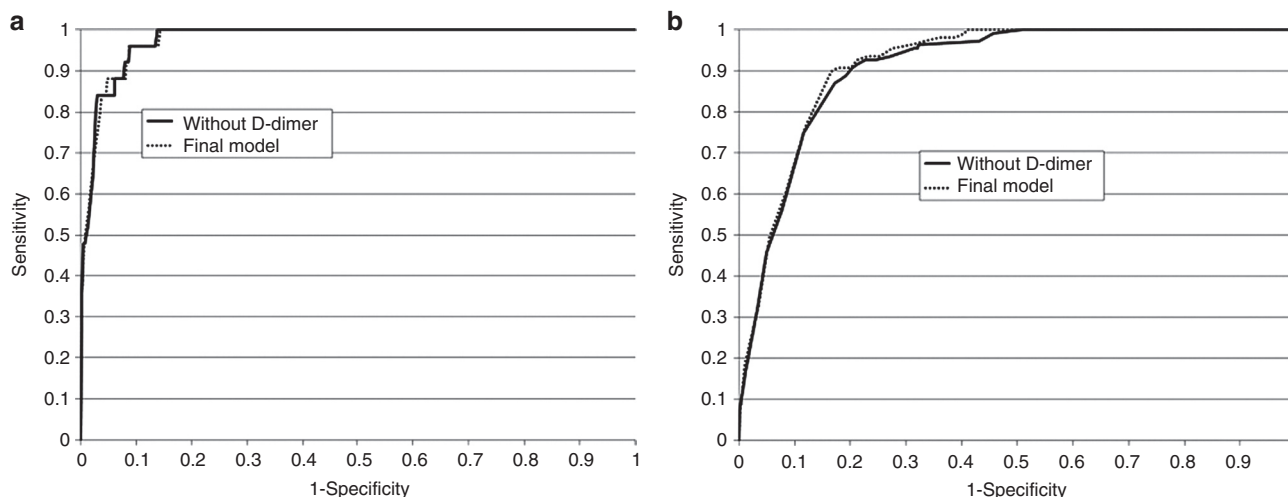


Figure 2 Receiver operating characteristic curves for whether abdominal aortic aneurysms is observed as (a) ≥ 50 mm or (b) ≥ 40 mm for the first time at the next observation for models with and without D-dimer covariate effects.

Table 4 Root mean square error of model predictions vs. data for the next AAA observation

Prior AAA size observations	Median root mean squared error (90% credible interval of median value)	
	Final model	No D-dimer effects
Overall, $N = 1,732$	2.51 mm (2.510, 2.514)	2.52 mm (2.519, 2.523)
Individual follow-up observations		
First follow-up, $N = 299$	2.55 mm (2.547, 2.553)	2.57 mm (2.568, 2.574)
Second follow-up, $N = 285$	2.67 mm (2.64, 2.72)	2.66 mm (2.63, 2.70)
Third follow-up, $N = 276$	2.51 mm (2.50, 2.52)	2.49 mm (2.48, 2.51)
Fourth follow-up, $N = 266$	2.51 mm (2.49, 2.54)	2.54 mm (2.52, 2.57)
Fifth follow-up, $N = 250$	2.41 mm (2.39, 2.44)	2.42 mm (2.39, 2.46)
Sixth follow-up, $N = 187$	2.34 mm (2.29, 2.40)	2.33 mm (2.28, 2.41)
Seventh follow-up, $N = 69$	2.52 mm (2.44, 2.62)	2.51 mm (2.41, 2.63)
Eighth follow-up, $N = 43$	2.40 mm (2.24, 2.58)	2.38 mm (2.22, 2.60)

AAA, abdominal aortic aneurysm.

individuals in this growth rate nearly averaged out on the population level. The data in this study are an example of how accounting for interpatient variability can influence model selection because the nonlinearity in AAA growth was seen at the individual level but not at the population level. We found that the hierarchical models with nonlinear effects had significantly lower deviance information criteria values than the linear model (7,113 for the linear model vs. 6,487 for the final model) suggesting a significantly better description of the data.

Similar to previous studies, AAA growth was found to be positively associated with the plasma D-dimer concentration¹⁷ and AAA diameter at screening^{14,15} but negatively associated with diabetes.^{17–20} Similar to the meta-analysis of Sweeting *et al.*,¹⁸ AAA growth was independent of age, sex, and mean arterial pressure. In contrast to the findings

of Sweeting *et al.*,¹⁸ we found no effect of smoking on AAA growth.

A log-transformation of plasma D-dimer concentration had the best association with growth rate model parameters suggesting that differences in AAA growth were predominantly driven by patients with the highest plasma D-dimer concentrations. This finding was reinforced by a sensitivity analysis in which plasma D-dimer values were categorized. This analysis demonstrated differences in the baseline growth rate model parameter only between patients with the lowest (≤ 150 ng/ml) and highest (>900 ng/ml) plasma D-dimer concentrations. The baseline AAA size measurement was also positively associated with the change in growth rate as well as the baseline growth rate. This result is internally consistent; because the baseline growth rate parameter was higher for larger AAAs, it follows that the growth rate would increase as size increased. Finally, diabetes was only associated with the first derivative of the growth rate with AAA size model parameter but not the baseline growth rate model parameter. In a previous study, Vega de Céniga *et al.*²⁰ found that diabetes was associated with slower AAA expansion only for AAAs with an initial size of 4–4.9 cm. It is possible that the effect of diabetes becomes more evident as AAAs increase in size which was difficult to be assessed in this study because most of the AAAs were < 4 cm. In patients with diabetes, Golledge *et al.*¹⁷ found a standardized regression coefficient of -0.17 between the overall growth rate and the diabetic status of the patient. We found no associations between growth rate and smoking or hypertension that have previously been reported as significant.^{15,18}

The population baseline growth rate model parameter of 1.32 mm/year was slower than the 2.60 mm/year and 2.81 mm/year growth rates reported in the UK Small Aneurysm Trial¹⁵ and the Chichester trial,¹⁴ respectively. This difference is most likely due to the smaller initial AAA sizes in the HIMS study relative to those in the other studies (32.7 vs. 43 mm of median baseline AAA size in HIMS vs. UK Small Aneurysm Trial, respectively). Adjusting for initial AAA size, the predicted initial growth rate of an AAA that was 43 mm at baseline is 1.98 mm/year, but this remains lower than the initial growth

rate reported in the UK Small Aneurysm Trial and Chichester studies. The reasons for these disparities remain unknown but could relate to differences in the population or methods of identifying subjects. Men included in this study were identified through screening rather than recruitment and they had to return for another blood sampling years after their initial diagnosis; it is possible that the cohort examined in this study is focused on more slowly growing AAAs, because those that were initially larger at diagnosis or grew faster would have already required AAA repair.

This study has several limitations. Foremost is that the D-dimer measurement was not collected at baseline and only measured at one time point. Therefore, the precise value of D-dimer in predicting AAA growth is not clear from this study; we found that D-dimer was indicative of AAA that did grow and not necessarily an AAA that will grow. In addition, while AAA growth rate was associated with D-dimer level, it is possible that the plasma D-dimer was associated with the larger size rather than the growth rate. A post hoc analysis found a small, positive correlation between the final AAA size observations and the D-dimer measurements (Pearson's $r = 0.26$). Longitudinal measurements of D-dimer are needed to determine whether D-dimer varies with AAA size or instantaneous growth rate. It is possible that longitudinal measures of plasma D-dimer could be predictive of instantaneous AAA growth. The study was also conducted in a single geographic location with a predominantly white population, on males only, and on small, screen-detected AAAs. The generalizability of the findings to other patient populations and to non-screen detected or large AAA is uncertain. The predictive ability of the model was also tested on surveillance intervals of mostly 0.5- or 1-year intervals and the accuracy for longer intervals is unknown. Finally, because of the relatively small sample size of the cohort, the accuracy of the predictions was tested on the same sample used for model development. The accuracy of the model when applied to an external cohort is unknown.

METHODS

Study setting and participants. The cohort of men included in this study consists of individuals who had a small (30–49 mm) AAA identified during the HIMS screening for AAA; had a follow-up ultrasound scan for surveillance of AAA; and provided a blood sample during the HIMS follow-up survey which was previously used to measure plasma D-dimer. Details of the design of the HIMS screening study and follow-up survey have previously been reported.^{17,21,22} Briefly, men included in the HIMS were originally part of a population screening study for AAA in Perth, Western Australia. The study was conducted from 1996 to 1999 and involved men of age 65–83 years. These men received an ultrasound for AAA screening and completed a history and lifestyle survey. Men were followed up as part of the HIMS between 2001 and 2004. Surviving men from the screening cohort were invited to provide a blood sample. The Human Research Ethics Committee at the University of Western Australia approved the ethics of the HIMS, and all subjects provided written and informed consent before participating in the study. The data analysis

protocol for this study was approved by the Indiana University Institutional Review Board.

AAA imaging. AAA size was measured as the greatest diameter of the infrarenal aorta using ultrasound (Toshiba Capasee with a 3.75 MHz probe, Toshiba Australia, North Ryde, Australia). The reproducibility of ultrasound measurements and interobserver variability were assessed every 4 months by re-imaging randomly selected patients. As previously reported, there were no significant differences between observers, and 95% of the measurement differences were <3 mm.⁷ AAA surveillance via ultrasound imaging was recommended every 6 months for patients with AAA ≥ 40 mm in diameter or every 12 months for patients with AAA diameter of 30–39 mm. Referral for consideration of surgical intervention was recommended for patients with AAA ≥ 50 mm.

Risk factors. At the time of AAA identification, all men completed a questionnaire designed to collect relevant patient history and lifestyle factors. The questionnaire assessed self-reported smoking status and number of cigarettes; history of, or treatment for, coronary heart disease, peripheral arterial disease, hypertension, stroke, dyslipidemia, and diabetes; and family history of AAA (first-degree relatives only). Age, height, weight, blood pressure, and the circumference of hips and waist of subjects were also measured.

Blood assays. Blood was collected between 2001 and 2004, and serum and plasma were isolated and stored at -80°C . Plasma D-dimer was measured by enzyme-linked immunosorbent assay as previously described.¹⁷ The interassay coefficient of variation for plasma D-dimer concentrations was 2–3%. Serum glucose, creatinine, total cholesterol, triglycerides, high-density lipoprotein, low-density lipoprotein, homocysteine, and C-reactive protein were measured by automated assays as previously reported.^{23,24}

Model of AAA growth. A hierarchical Bayesian model with individual-level growth parameters was fitted to the serial AAA size data using WinBUGS 1.4.3²⁵ software (see **Supplementary Data** online) called from R using the R2WinBUGS package.²⁶ Five chains were used for each analysis with each chain having a burn-in period of 10,000 iterations and postburn-in period of 20,000, keeping every 10th sample for a total sample of 10,000 iterations. Gelman–Rubin diagnostics were used to confirm convergence of the model (see **Supplementary Figures S1 and S2** online).

The base (or covariate free) model was selected by comparing the deviance information criteria and parameter CrI among several potential model structures. The candidates included models with a constant growth rate with time; a growth rate whose first derivative with time was a constant rate, a linear function of time, and a linear function of AAA size; and a growth rate whose first derivative with size was a constant rate. The following differential equations give the expected AAA diameter, $\bar{Y}_{i,k}(t)$, for the k th MCMC iteration applied to the i th individual as a function of time. The predicted AAA diameter at this time, $\hat{Y}_{i,k}(t)$, is assumed to be normally distributed about the expected value where $\varepsilon \sim N(0, \sigma_{\varepsilon}^2)$ is the amount of deviation.

Constant AAA growth rate. Individual-level baseline size, $\beta_{0,k}^{(i)}$, and growth rate, $\beta_{1,k}^{(i)}$, parameters

$$\frac{d\bar{Y}_{i,k}(t)}{dt} = \beta_{1,k}^{(i)}, \quad \bar{Y}_{i,k}(0) = \beta_{0,k}^{(i)}$$

or

$$\hat{Y}_{i,k}(t) = \beta_{0,k}^{(i)} + \beta_{1,k}^{(i)}t + \varepsilon$$

First derivative of the AAA growth rate with time is constant. Individual-level baseline size, $\beta_{0,k}^{(i)}$, baseline growth rate, $\beta_{1,k}^{(i)}$, and constant first derivative of AAA growth rate with time, $\beta_{2,k}^{(i)}$, parameters

$$\frac{d\bar{Y}_{i,k}(t)}{dt} = r_{i,k}(t), \quad \bar{Y}_{i,k}(0) = \beta_{0,k}^{(i)}$$

$$\frac{dr_{i,k}(t)}{dt} = 2\beta_{2,k}^{(i)}, \quad r_{i,k}(0) = \beta_{1,k}^{(i)}$$

or

$$\hat{Y}_{i,k}(t) = \beta_{0,k}^{(i)} + \beta_{1,k}^{(i)}t + \beta_{2,k}^{(i)}t^2 + \varepsilon$$

First derivative of AAA growth rate with time is a linear function of time. Individual-level baseline size, $\beta_{0,k}^{(i)}$; baseline growth rate, $\beta_{1,k}^{(i)}$; and constant, $\beta_{2,k}^{(i)}$, and linear, $\beta_{3,k}^{(i)}$, rates of change in AAA growth rate with time

$$\frac{d\bar{Y}_{i,k}(t)}{dt} = r_{i,k}(t), \quad \bar{Y}_{i,k}(0) = \beta_{0,k}^{(i)}$$

$$\frac{dr_{i,k}(t)}{dt} = 2\beta_{2,k}^{(i)} + 6\beta_{3,k}^{(i)}t, \quad r_{i,k}(0) = \beta_{1,k}^{(i)}$$

or

$$\hat{Y}_{i,k}(t) = \beta_{0,k}^{(i)} + \beta_{1,k}^{(i)}t + \beta_{2,k}^{(i)}t^2 + \beta_{3,k}^{(i)}t^3 + \varepsilon$$

First derivative of the AAA growth rate with time is a linear function of AAA size. Individual-level baseline size, $\beta_{0,k}^{(i)}$; baseline growth rate, $\beta_{1,k}^{(i)}$; and constant, $\beta_{2,k}^{(i)}$, and a positive linear with size, $\beta_{3,k}^{(i)}$, rates of change in AAA growth rate with time

$$\frac{d\bar{Y}_{i,k}(t)}{dt} = r_{i,k}(t), \quad \bar{Y}_{i,k}(0) = \beta_{0,k}^{(i)}$$

$$\frac{dr_{i,k}(t)}{dt} = \beta_{2,k}^{(i)} + \beta_{3,k}^{(i)}\bar{Y}_{i,k}(t), \quad r_{i,k}(0) = \beta_{1,k}^{(i)}$$

or

$$\hat{Y}_{i,k}(t) = \left(\beta_{0,k}^{(i)} - \frac{\sqrt{\beta_{3,k}^{(i)}\beta_{0,k}^{(i)} - \beta_{1,k}^{(i)}}}{\sqrt{\beta_{3,k}^{(i)} + 1}} \right) \exp\left[\sqrt{\beta_{3,k}^{(i)}}t\right]$$

$$- \frac{\sqrt{\beta_{3,k}^{(i)}\beta_{0,k}^{(i)} - \beta_{1,k}^{(i)}}}{\sqrt{\beta_{3,k}^{(i)} + 1}} \exp\left[-\sqrt{\beta_{3,k}^{(i)}}t\right] + \beta_{2,k}^{(i)}t^2 + \varepsilon$$

First derivative of AAA growth rate with size is constant. Individual-level baseline size, $\beta_{0,k}^{(i)}$, baseline AAA growth rate, $\beta_{1,k}^{(i)}$, and constant first derivative of AAA growth rate with size, $\beta_{2,k}^{(i)}$.

$$\frac{d\bar{Y}_{i,k}(t)}{dt} = r_{i,k}(\bar{Y}_{i,k}(t)), \quad \bar{Y}_{i,k}(0) = \beta_{0,k}^{(i)}$$

$$\frac{dr_{i,k}(\bar{Y}_{i,k}(t))}{dx} = \beta_{2,k}^{(i)}, \quad r_{i,k}(\bar{Y}_{i,k}(0)) = \beta_{1,k}^{(i)}$$

or

$$\hat{Y}_{i,k}(t) = \left(\beta_{0,k}^{(i)} + \frac{\beta_{1,k}^{(i)} - \beta_{2,k}^{(i)}\beta_{0,k}^{(i)}}{\beta_{2,k}^{(i)}} \right) e^{\beta_{2,k}^{(i)}t} - \frac{\beta_{1,k}^{(i)} - \beta_{2,k}^{(i)}\beta_{0,k}^{(i)}}{\beta_{2,k}^{(i)}} + \varepsilon$$

The regression parameters for an individual patient $\beta_k^{(i)} = [\beta_{0,k}^{(i)}, \beta_{1,k}^{(i)}, \dots, \beta_{n,k}^{(i)}]$ are selected from a multivariate normal distribution $\beta_k^{(i)} \sim N(\bar{\beta}_k^{(i)}, \Sigma)$ where $\bar{\beta}_k^{(i)}$ is the vector of expected parameter values for k th MCMC parameter set to the covariate effects of the i th individual and Σ is the covariance matrix. Noninformative normal distributions were used as prior distributions for the parameters, a Wishart distribution for parameter precisions, and an inverse gamma distribution for the precision of the normally distributed residual error.

After selection of the base model structure, covariate effects on model parameters were tested using a stepwise forward addition and backward elimination method. Additive, proportional, and power functions were tested for each continuous covariate and additive and proportional functions were tested for each discrete covariate (see **Table 1** for patient demographic, medical conditions, and blood measurement covariates tested). In addition, plasma D-dimer was also tested as a discrete covariate by grouping according to concentration (≤ 150 , 151–300, 301–900, and >900 ng/ml). Covariate effects whose 95% CrIs did not cross 0 in single covariate analyses were included in an intermediate model. Covariate effects whose 95% CrIs did not cross 0 in the intermediate model were eliminated and additional iterations of the forward addition and backward elimination were performed until there were no changes.

When the baseline size measurement was included as a covariate on model parameters, this measurement was not used in the Bayesian analysis. In other words, the baseline size measurement was used to adjust model parameters either through covariate effects or in a Bayesian manner but not both.

Accuracy of AAA size predictions

To quantify the predictive capability of the final model, we calculated the RMSE and the area under the ROC curve of the model-predicted likelihood that an AAA was at least 40 mm (after which the surveillance interval was reduced from 12 to 6 months) or 50 mm (after which referral for consideration of surgical intervention was recommended) at the next observation. To assess the added value of D-dimer for predicting AAA size observations, we compared these outcomes for the final model, which includes patient-specific D-dimer measurements, vs. those for a model without plasma D-dimer effects.

The RMSE compared AAA size measurements—where $Y_{i,j}$ and $t_{i,j}$ were the observed AAA size truncated to the nearest 0.1 mm and amount of time after the screening observation, respectively, for the j th observation of the i th individual, N_i was the number of AAA size observations of the i th individual, and x_i was the vector of covariate measurements for the i th individual—with the corresponding model-predicted size truncated to the nearest 0.1 mm, $\hat{Y}_{i,j,k}^{(0.1\text{mm})}$ using the k th MCMC parameter set, and β_k , output from WinBUGS. The model predictions for j th observation were conditional on all previous size observations because the likelihood of a particular parameter set was conditional on the prior observations

$$\text{RMSE} = \left(\frac{\sum_{i=1}^{299} \sum_{j=1}^{N_i} \sum_{k=1}^{10,000} \Pr(\beta_k | Y_{i,j-1}, \dots, Y_{i,1}; t_{i,j-1}, \dots, t_{i,1}; x_i)}{\sum_{i=1}^{299} \sum_{j=1}^{N_i} 1} \left(Y_{i,j} - \hat{Y}_{i,j,k}^{(0.1\text{mm})} | t_{i,j}; \beta_k; x_i \right)^2 \right)^{1/2}$$

A particular value of $\hat{Y}_{i,j,k}^{(0.1\text{mm})} | t_{i,j}; \beta_k; x_i$ was randomly sampled based on the approximation of MCMC iterations of the posterior predictive distribution

$$\begin{aligned} & \Pr\left(\hat{Y}_{i,j,k}^{(0.1\text{mm})} | t_{i,j}; \beta_k; x_i\right) \\ &= \Pr\left(y \leq \hat{Y}_{i,j,k} | t_{i,j}; \beta_k; x_i < y + 0.1\text{mm}\right) \end{aligned}$$

where y is in 0.1 mm increments beginning at 0 and

$$\Pr\left(\beta_k | Y_{i,j-1}, \dots, Y_{i,1}; t_{i,j-1}, \dots, t_{i,1}; x_i\right) = \frac{\prod_{j=1}^{j-1} \Pr\left(y \leq \hat{Y}_{i,j',k}^{(0.1\text{mm})} = Y_{i,j'} | t_{i,j'}; \beta_k; x_i < y + 0.1\text{mm}\right)}{10,000 \sum_{k=1}^{10,000} \prod_{j=1}^{j-1} \Pr\left(y \leq \hat{Y}_{i,j',k}^{(0.1\text{mm})} = Y_{i,j'} | t_{i,j'}; \beta_k; x_i < y + 0.1\text{mm}\right)}$$

The RMSE calculation was replicated 1,000 times to determine a 90% CrI about the median value. The RMSE for a specific observation number (i.e., value of j) was also retained if there were at least 40 observations.

The ROC curve was generated based on clinical observations for two outcomes used during the HIMS: the likelihood of a first size observation of at least 40 mm and the likelihood of a first size observation of at least 50 mm. After a particular value of $\hat{Y}_{i,j}$ was selected, this value was compared with both 40 and 50 mm. For the 40 mm threshold, the model-predicted probability that the AAA size at a particular observation was >40 mm was the fraction of simulations for that observation that was >40 mm. To generate the ROC curve, the threshold above which the model-predicted probability of being >40 mm was defined as “predicting” this size was varied and the actual observation of whether AAA was at least 40 mm at the next observation with the model prediction. Observations for patients with AAA that had already crossed 40 mm were excluded from that analysis. An analogous approach was used for the 50 mm threshold.

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Conflict of interest. The authors declared no conflict of interest.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

There is considerable interindividual variability in AAA growth, and plasma D-dimer concentration is associated with growth.

WHAT QUESTION DID THIS STUDY ADDRESS?

This study sought to develop a hierarchical, Bayesian model that describes growth of small AAA and then to determine whether the model can accurately predict AAA size at the next observation.

WHAT THIS STUDY ADDS TO OUR KNOWLEDGE

A nonlinear growth model for AAA in which the growth rate changes as AAA grow or shrink best fitted the data. This model has advantages of being consistent with the baseline AAA size covariate effect and not relying on temporal growth rate changes. The model accurately predicted whether an AAA would be ≥ 40 or ≥ 50 mm at the next surveillance observation.

HOW THIS MIGHT CHANGE CLINICAL PHARMACOLOGY AND THERAPEUTICS

This model could potentially be used to tailor surveillance intervals based on model-predicted risk. We found that, although plasma D-dimer was associated with AAA growth, there was little added value of a single plasma D-dimer concentration for predicting AAA size.

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