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Comparison of peak wall stress in ruptured, symptomatic and intact abdominal aortic aneurysms: A systematic review and meta-analysis.

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ABSTRACT

Background Abdominal aortic aneurysm (AAA) is an important cause of sudden death however there are currently incomplete means to predict AAA rupture risk. AAA peak wall stress (PWS) can be estimated using finite element analysis (FEA) methods from Computed Tomography (CT) scans. Whether AAA PWS predicts AAA rupture is not yet firmly established. The aim of this systematic review was to compare PWS in patients with ruptured and intact AAAs.

Method: We performed a search of the MEDLINE database on the 25th May 2013. Case-control studies assessing PWS in asymptomatic intact, and acutely symptomatic or ruptured AAAs from CT scans using FEA were included. Data were independently extracted. A random effects model was used to calculate standardized mean differences (SMDs) for PWS measurements in patients with asymptomatic intact and symptomatic or ruptured AAAs.

Results: Nine studies assessing 348 individuals were identified and used in the meta-analysis. Results from 204 asymptomatic intact and 144 symptomatic or ruptured AAAs showed that PWS was significantly greater in the symptomatic/ ruptured AAAs compared to the asymptomatic intact AAAs (SMD: 0.95; 95% CI: 0.71-1.18; $p < 0.001$). The findings remained significant after adjustment for the mean systolic blood pressure, standardised at 120 mmHg (SMD: 0.68, 95% CI: 0.39-0.96, $p < 0.001$). Minimal heterogeneity between studies was noted ($I^2 = 0\%$).

Conclusion: This study suggests that PWS is greater in symptomatic or ruptured AAAs than asymptomatic intact AAAs. This finding supports a potential role for PWS in AAA rupture prediction.

INTRODUCTION

Abdominal aortic aneurysm (AAA) is a progressive focal dilatation and weakening of the abdominal aorta and is associated with a risk of fatal rupture. Important risk factors for AAA are advanced age, male gender, smoking and family history¹⁻³. The latest results of The National Health Service Abdominal Aortic Aneurysm Screening Program suggest that the prevalence of AAAs is 1.8% in men aged 65-74 years within England⁴. AAAs are usually asymptomatic but AAA rupture has a mortality of approximately 65-85%⁵. In the absence of effective drugs, surgical repair is the only available treatment for AAA. AAA management is largely determined by maximum AAA diameter which is routinely monitored through medical imaging assessments⁶. Surgical repair is usually considered when the maximum AAA diameter is >55mm as below this diameter elective surgical repair has been shown not to reduce mortality³. However, rupture of AAAs measuring less than 55mm has been reported, suggesting that the risk of rupture is not determined by aortic diameter alone^{1,3}. In the UK Small Aneurysm Trial (UKSAT) the annual rate of AAA rupture was 2.2% after a 3 year follow-up period³. Additional means of selecting patients for prophylactic AAA repair could prevent more AAA ruptures. The RESCAN collaborators recently reported that the rupture rate of small AAAs was fourfold higher in women, double in smokers and increased with higher mean arterial blood pressure, suggesting these additional measures should be considered when selecting patients for AAA repair⁷.

The precise mechanisms leading to AAA rupture remain unclear, however a biomechanical wall stress which exceeds the mechanical strength of the weakened arterial wall is thought to be the final common pathway⁸. Consequently, the highest wall stress within an AAA, i.e. peak wall stress (PWS), has been suggested to indicate risk of rupture. Factors that influence PWS include blood pressure, aneurysm geometry, vessel wall stiffness, wall thickness, the shape and characteristics of the intra-luminal thrombus (ILT) and are highly patient specific. ILT is present in about 75% of all AAAs and the volume of ILT has been suggested to alter PWS by multiple means and is also associated with AAA growth rates⁹⁻¹².

PWS can be estimated non-invasively from computed tomography (CTs) scans using finite element analysis (FEA; Figure 1). This approach has been used previously to examine the association of PWS with aortic rupture however interpretation of the information is complicated by small sample

sizes and heterogeneity between studies ¹³⁻¹⁵. A systematic review was performed of publicly available literature to examine the current evidence supporting the use of PWS for predicting AAA rupture. Specifically the aim of this review was to compare PWS in patients with symptomatic or ruptured and asymptomatic intact AAAs. A meta-analysis was performed to combine the results from studies that measured PWS in patients with symptomatic or ruptured and asymptomatic intact AAAs.

METHODS

Literature search

A search strategy was devised according to the 2009 preferred reporting items for systematic reviews and meta-analysis statement¹⁶. A search of the MEDLINE (January 1966–May 2013) database was performed on the 25th May 2013. In order to identify studies assessing the association between PWS and AAA rupture, the following search terms were applied: ('abdominal aortic aneurysm' OR 'AAA')[Title/Abstract] AND ('rupture' OR 'rupture risk')[Title/Abstract] AND ('peak wall stress' OR 'stress' OR 'shear stress' OR 'biomechanic*')[Title/Abstract]. No language restrictions were used. In addition, reference lists of primary articles and reviews were searched to increase the yield of relevant publications. Titles and abstracts were screened to identify potentially relevant studies. If the suitability of an article was uncertain the full text was assessed. To be eligible, studies were required to have compared PWS in patients with asymptomatic intact and ruptured AAAs. Studies which recruited patients with symptomatic AAAs that required urgent repair were also included. Included studies had to use FEA to measure PWS from CT scans. Studies were excluded if: AAAs were not assessed by abdominal CT imaging; there was no clear division of patients into ruptured/symptomatic and intact groups; ex-vivo methods to analyse biomechanical wall properties were used.

Data extraction and quality assessment

Data were extracted from included studies by one author (SK) using set criteria and recorded in tables. Extracted data were independently reviewed by three other authors (DRM, JVM and JG). Any inconsistencies in data were recorded and resolved by discussion. The following data were recorded: Definitions used for symptomatic, ruptured and asymptomatic intact AAA; the timing of the CT scan relative to AAA rupture; population characteristics; details of the FEA methodology used; and the value of PWS at both population and standardized SBP. Methodological quality was assessed using a modified version of the QUADAS-2 quality assessment tool¹⁷. Quality measures included a description of patient characteristics, the timing of CT scan relative to rupture, the measurement of PWS at standardized systolic blood pressure (SBP) of 120 mmHg, the incorporation of intra-luminal thrombus in calculating PWS and the sample size used. The quality of studies was categorized as good, fair or poor. Good quality studies were those with a case-controlled design that had a minimum of 20 individuals in each group, reported at least 3 major risk

factors for AAA rupture including maximum AAA diameter, gender, age or smoking history, reported PWS at both population and standardized SBP of 120 mmHg and included CTs performed prior to the time of AAA rupture for the ruptured group. Fair quality studies required all of the above except a smaller sample size of 10-20 patients in both groups and did not necessarily include pre-rupture CTs for the ruptured group. Studies of poor quality had fewer than 10 patients in each group and failed to report a minimum of 3 major risk factors for AAA rupture including maximum AAA diameter, gender, age or smoking history, even if they used pre-rupture scans.

Statistical analysis

A meta-analysis was performed comparing PWS in patients with asymptomatic intact and ruptured (or symptomatic) AAAs. Some studies combined patients with symptomatic AAAs with those with ruptured AAAs^{19-20, 22}. Four studies reported PWS as mean \pm standard deviation and the remaining 5 studies reported mean \pm standard error. Data were imported into the Review Manager (RevMan) v5.2 software package. Standard deviations were calculated automatically for studies which cited standard error only by the RevMan software. PWS was compared between groups of patients with intact and ruptured AAA for each study included via 2-sample t-test (RevMan). Standardised mean differences (SMDs) and 95% confidence intervals (CIs) were calculated for each included study. Study specific estimates were combined using inverse variance weighted average of logarithmic SMDs in a random effects model. The random effects model was used to reduce the effect of heterogeneity in FEA methods on the summary statistics. A further analysis was performed to analyse the PWS in the two groups at standardized SBP. An assessment of inter-study heterogeneity was performed using the I^2 index. Sensitivity analyses were performed to assess the contribution of each study to the pooled estimate by excluding individual studies one at a time and recalculating the pooled SMD estimates for the remaining studies. Publication bias was assessed using a funnel plot of the logarithm of effect size versus the standard error for each study but could not be accurately appraised because of the limited number of studies.

RESULTS

Study selection

Initial database searches yielded 67 potentially eligible studies (Figure 2) including 3 additional studies that were identified by hand searching the reference lists. Forty-five articles were excluded based on review of article titles and abstracts. The main reason for exclusion was the lack of clear division of AAA patients into asymptomatic intact and symptomatic or ruptured groups. Of the 22 full text studies that were evaluated for inclusion in the meta-analysis, 13 were excluded as they used ex-vivo methods of measuring biomechanical wall properties. The remaining 9 studies were included in this review¹⁸⁻²⁶.

Study characteristics

The studies assessed populations mainly from the USA and Europe. All studies used CT scans as the imaging modality for AAA visualization. Study characteristics and methodological quality of included studies are shown in supplementary Table 1.

One of the 9 studies did not present a clear description of the inclusion criteria for the 2 groups of AAA patients²⁴. In patients with symptomatic/ ruptured AAA, PWS was assessed from CT scans performed before the onset of acute symptoms or rupture in 5 studies^{18, 21, 22, 25, 26} and after the onset of acute symptoms or rupture in 3 studies^{19, 20, 23}. For one study it was unclear whether CT scans used were obtained before or after the onset of acute symptoms or rupture²⁴. Five of the 9 studies estimated PWS in the intact and ruptured groups at a SBP of 120 mmHg^{18, 20, 22-24}. Four of the 9 studies considered ILT volume in their calculation of PWS using FEA^{19, 21, 25, 26}.

The reporting of risk factors was not uniform across studies. Maximal aortic diameter was reported by 8 studies, overall the average diameter of intact AAAs ranged from 51 to 70mm whereas ruptured AAAs had average diameters between 53 and 81mm. Two studies did not report the age of included patients^{21, 25}. Data from the remaining studies suggested that the average age of the studied patients ranged from roughly 69 to 77 years. Seven studies provided details of patient gender, 5 of which noted a higher proportion of females in the ruptured groups^{18, 19, 22, 23, 26}. The proportion of smokers appeared to be higher in the ruptured groups in 4 of the 5 studies detailing patient smoking history^{18, 20, 22, 24}. The population maximum blood pressure was higher in the ruptured groups in 4

of the 5 studies^{18, 20, 22, 23} that reported this risk factor. In 3 of the 5 studies, the prevalence of atherosclerotic cardiac disease was higher in the intact aneurysms compared to ruptures^{18, 22, 23}.

Sample sizes of the included studies ranged from 5 to 40 patients in the intact groups and 8 to 30 in the ruptured groups (Supplementary Table 1). The symptomatic patients were defined as patients presenting with acute abdominal pain requiring emergency surgery and were included in the ruptured group for comparison with asymptomatic intact AAAs. Four of the 9 studies reported PWS for symptomatic patients^{18, 19, 20, 22} but only 3 of these included symptomatic patients in the ruptured group when reporting the PWS and were included in the meta-analysis^{19, 20, 22}. The fourth study reported PWS separately for intact, symptomatic (n=8), and ruptured (n=10) AAAs¹⁸. For the purposes of this meta-analysis, we used the PWS in the ruptured group in the latter study only (n=10)¹⁸. A combined population of 348 individuals (representing 204 asymptomatic intact and 144 symptomatic/ruptured AAAs) was included in the meta-analysis (Table 1).

As some studies reported p-values from comparisons of PWS in >2 groups of patients extracted data were reanalyzed via 2 sample t-test in order to directly compare groups of patients with intact and ruptured AAAs and to standardize statistical comparisons between studies. In all studies mean PWS was higher in patients with symptomatic or ruptured AAAs compared to patients with intact AAAs (Table 1)¹⁸⁻²⁶, but was not statistically significant in 2 studies^{21, 25}. Both of these studies had small sample sizes of less than 10 patients in each group and were found to be of poor quality using the quality assessment tool (Supplementary Table 1)^{21, 25}. Five of the 9 studies compared PWS between groups of patients with intact and ruptured AAAs using standardizing blood pressure of 120 mmHg. At standardized systolic blood pressure, PWS remained higher in the patients with ruptured AAA compared to those with intact AAA, although statistical significance was only demonstrated by 4 studies after this adjustment (Table 1)^{18, 20, 22, 24}.

Data synthesis

Three of the 9 studies combined the symptomatic and ruptured groups as one for comparing PWS with the intact group.^{19, 20, 22} One study defined the symptomatic group of patients as those with an acute or leaking AAA, and these patients were considered to have ruptured AAAs due to high probability of rupture²⁰. Two^{20, 24} of the 9 studies reported the results in MegaPascals (MPa), 2

studies^{19, 26} reported in kilopascals (kPa) whilst the remaining studies used Newton/cm² (N/cm²). All measurements in MPa and kPa were converted to N/cm² according to the following relationship: 1MPa = 1000kPa = 100N/cm² (Table 1). A meta-analysis of the 9 studies (representing 204 asymptomatic intact and 144 symptomatic/ruptured AAAs) demonstrated significantly higher PWS in the ruptured group than in the intact group using a random-effects model (SMD: 0.95; 95% CI: 0.71-1.18; p <0.001; Figure 3). Analyses suggested that there was little heterogeneity between the included studies (I²=0%). Sensitivity analyses demonstrated that multiple studies contributed to the observed difference in PWS between the 2 groups and the exclusion of any single study from the analysis did not substantively alter the overall result of the analysis (Supplementary Table 2). A further analysis of PWS measured at SBP of 120 mmHg in 218 AAAs (including 134 intact and 84 symptomatic/ruptured AAAs) demonstrated that PWS remained significantly higher in the symptomatic/ruptured group in comparison to the intact group (SMD: 0.68, 95% CI: 0.39-0.96, p<0.001) even when accounting for SBP (Table 1 and Figure 4). No significant heterogeneity was observed between the studies included in this sub-analysis (I²=0%).

DISCUSSION

PWS has been suggested as a measure to estimate AAA rupture risk. PWS has been documented to be higher in ruptured than intact AAAs in a number of independent studies, although this difference was only significant in 7 of the 9 studies^{18-20, 22-24, 26}. The results from these small studies has been combined in the current analysis which suggests that PWS is higher in patients with symptomatic or ruptured compared to intact AAAs, even if assessed at a standardized SBP of 120mmHg. Confidence in these findings is restricted due to the overall size of both groups which was not substantial.

This analysis must be viewed in the context of its limitations. First, there was qualitative heterogeneity in participant selection among included studies and the FEA software used to analyse CT scans. Three studies combined symptomatic and ruptured AAAs and compared these with the asymptomatic intact AAAs^{19, 20, 22}. Secondly, heterogeneity in the timing of the CT relative to the time of rupture was observed. Five of the 9 studies assessed CTs generated prior to the rupture event for calculating PWS in the ruptured group^{18, 21, 22, 25, 26} whereas 3 studies used CTs performed at the time of the rupture prior to surgical repair^{19, 20, 23}, when the patients were in a stable condition. Which approach is likely to be more representative of PWS at the time of rupture is unclear. Differences were also observed in the FEA calculations applied to calculate PWS in the included studies and the units that PWS was reported in. In this review all PWS reported were uniformly converted into N/cm² to allow easier comparison. Moreover, the random effects model was used to calculate a standardized mean difference in PWS between the ruptured/symptomatic and intact AAAs. This model was used to minimise the influence of heterogeneity between studies on the meta-analysis, as suggested by The Cochrane Collaboration guidelines²⁷. The results from the meta-analysis indicate that PWS is likely to be higher in symptomatic/ruptured than intact AAAs. This finding is supported by observational studies performed to assess if PWS increases with increasing AAA size. For example, Fillinger *et al.* followed 103 patients with small AAAs and found that the initial peak wall stress determined through FEA, was 38 N/cm² for aneurysms that remained stable during the observation period of 14 months, compared to 42 N/cm² for expanding aneurysms and 58 N/cm² for aneurysms that ultimately ruptured²².

It is well established that smaller diameter AAAs can rupture^{3,7,28}. FEA has gained significant credibility as a reliable measure for calculating PWS, however this technique relies on some

standard assumptions of AAA wall thickness and stiffness, based on previous autopsy studies^{13,29}. Most software packages use a standard wall thickness of 2 mm for all patients, which is not specific to each case. The aneurysmal aorta is assumed to be homogeneous with linear elastic properties. Based on experimental findings suggesting that the mechanical properties of circumferentially and longitudinally oriented aortic tissues do not differ²⁹ isotropic material properties are used to estimate PWS. To accurately estimate PWS the strength of the wall should be mechanically tested on excised tissues from various regions of the same aorta to account for localized differences in vessel biology.

Another concern with the use of commercially available semi-automated FEA programs is the variability in results between different software packages. A recent investigation studied the inter- and intra-observer variability of a semiautomatic diagnostic software (A4research, VASCOPS GmbH, Graz, Austria) to measure PWS in AAAs³⁰. The inter-observer reproducibility for the three observers showed an interclass coefficient (ICC) of 0.98 (range: 0.97-0.99) for PWS. Not all models have been tested for inter- observer variability, limiting the confidence in PWS estimated with some models.

Finally, although simple geometrical properties can be used to calculate PWS, the use of FEA provides more accurate results as it also incorporates ILT, AAA geometry, wall stiffness and blood pressure^{15,30-31}. The presence of calcification and ILT has been shown to increase AAA PWS, suggesting both should be considered in the evaluation of wall stress for assessment of AAA rupture risk^{9, 31}. However, the use of calcification in FEA also requires calculating the resultant reduction in wall strength at the site of calcification to accurately estimate PWS which is problematic²⁶. It has been suggested that PWS measurements can add substantially to rupture prediction performed by diameter alone^{13, 19, 22, 26}. Fillinger *et al* showed that PWS was superior to diameter in predicting catastrophic events in patients with AAAs under observation²². Receiver operating characteristics (ROC) curves for predicting rupture showed PWS to have higher sensitivity, specificity and accuracy (94%; 81%; 85% (with 44N/cm² threshold)) than diameter (81%; 70%; 73% (with 55mm threshold))²². PWS is considered to be a direct function of critical factors such as patient age, sex, blood pressure, AAA size and shape as it incorporates AAA geometry and blood pressure in the calculation^{13, 29}. PWS analysis is most likely to benefit the management of small aneurysms (<55mm) through the identification of patients that are unsuitable

for observation due to a high risk of AAA rupture. Fillinger *et al.*²² showed that the smallest aneurysm in their study to rupture had a maximum diameter of 44mm but had stress equivalent to a typical AAA twice the size. AAAs do not necessarily rupture at the site of maximum diameter. In keeping with this, PWS is often higher at points proximal or distal to the point of maximum diameter (Figure 1). PWS may be useful at predicting AAA growth with previous studies suggesting that inflammatory activity assessed by PET/CT scans is high at sites of high PWS³². Further research is needed to examine the value of PWS in these areas.

Currently there are several biomechanical and post-processing FEA methods available for calculating PWS. The lack of a standardized technique to measure PWS using FEA limits the translation of this potentially beneficial predictor of AAA rupture into clinical practice. Until recently the calculation of PWS using FEA was an experimental method which was both time consuming and labor intensive, limiting its potential role in clinical practice. However, there are now a number of commercially available programs which streamline this process and enable analysis of standard CT images.

PWS may be beneficial in identifying high risk aneurysms that would benefit from early intervention. There are several areas that require improvement such as: Improving FEA modeling to incorporate calcification, which may increase PWS⁹; developing methods to non-invasively measure wall thickness to enable patient-specific PWS measurements; and testing the FEA models for inter- and intra-observer variability. If these improvements are made, a standardized technique with low user-dependent bias should be established in order to reliably estimate PWS and allow for assessment in future studies.

Ultimately, more research is required before the value of adding PWS measurements into clinical practice is clear. Ideally a large multicenter randomized controlled trial comparing clinical outcomes and cost-benefits when using PWS and diameter with use of diameter alone is required to determine whether PWS is clinically useful. Such a study would not be straightforward to undertake for many reasons, including the need to standardize clinical assessments across sites and the variation in decision making protocols at different centers.

This systematic review and meta-analysis of 9 studies comparing PWS in intact and symptomatic/ruptured AAAs suggests that the use of PWS as a surrogate marker for AAA rupture

is plausible. Further investigation of the geometrical and material properties that influence PWS may improve the ability to predict AAA rupture and assist in the development of a patient-specific biomechanical model to guide surgeons in addition to AAA diameter. However before this is possible, a standardized technique to measure PWS is required.

Competing Interests

Professor Gasser is the scientific advisor of VASCOPS GmbH.

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Supplementary material

Supplementary table 1 shows the characteristics and the quality of the included studies.

Supplementary table 2 shows the results of the leave-one-out sensitivity analyses.

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Figure Legends

Figure 1: Peak wall stress (PWS) measurement using finite element analysis. The areas are coloured according to the PWS exerted on the abdominal aortic aneurysm wall, with red representing the point of maximum PWS, followed by yellow, green and blue respectively as shown on the colour scale. Interestingly, the PWS is greater at a site that is not the point of maximum diameter. L, left; PWRR, peak wall rupture risk; max, maximum; Lmn, lumen; ext, external; v. Mises Stress: von Mises Stress.

Figure 2: Outline of the identification of studies. A total of 202 published articles were identified by searching the MEDLINE database. Three additional articles were identified by searching article references. Assessment of the abstracts identified 22 articles eligible for full-text appraisal. From these, a further 13 articles were excluded and the remaining 9 studies were included in the meta-analysis.

Figure 3: Forest plot illustrating higher PWS in the ruptured or symptomatic compared to intact AAAs. Measurements were made at SBP, except in the study done by Gasser *et al.* (which used mean arterial pressure (MAP)). Please note, the study by Venkatasubramaniam *et al.* has been abbreviated to 'Subramaniam' due to space constraints. Study-specific estimates were combined using inverse-variance (IV) weighted average of logarithmic SMDs in a random-effects model

Figure 4: Forest plot illustrating higher PWS in the ruptured or symptomatic compared to intact AAAs when estimated at a standardized SBP of 120. Please note, the study by

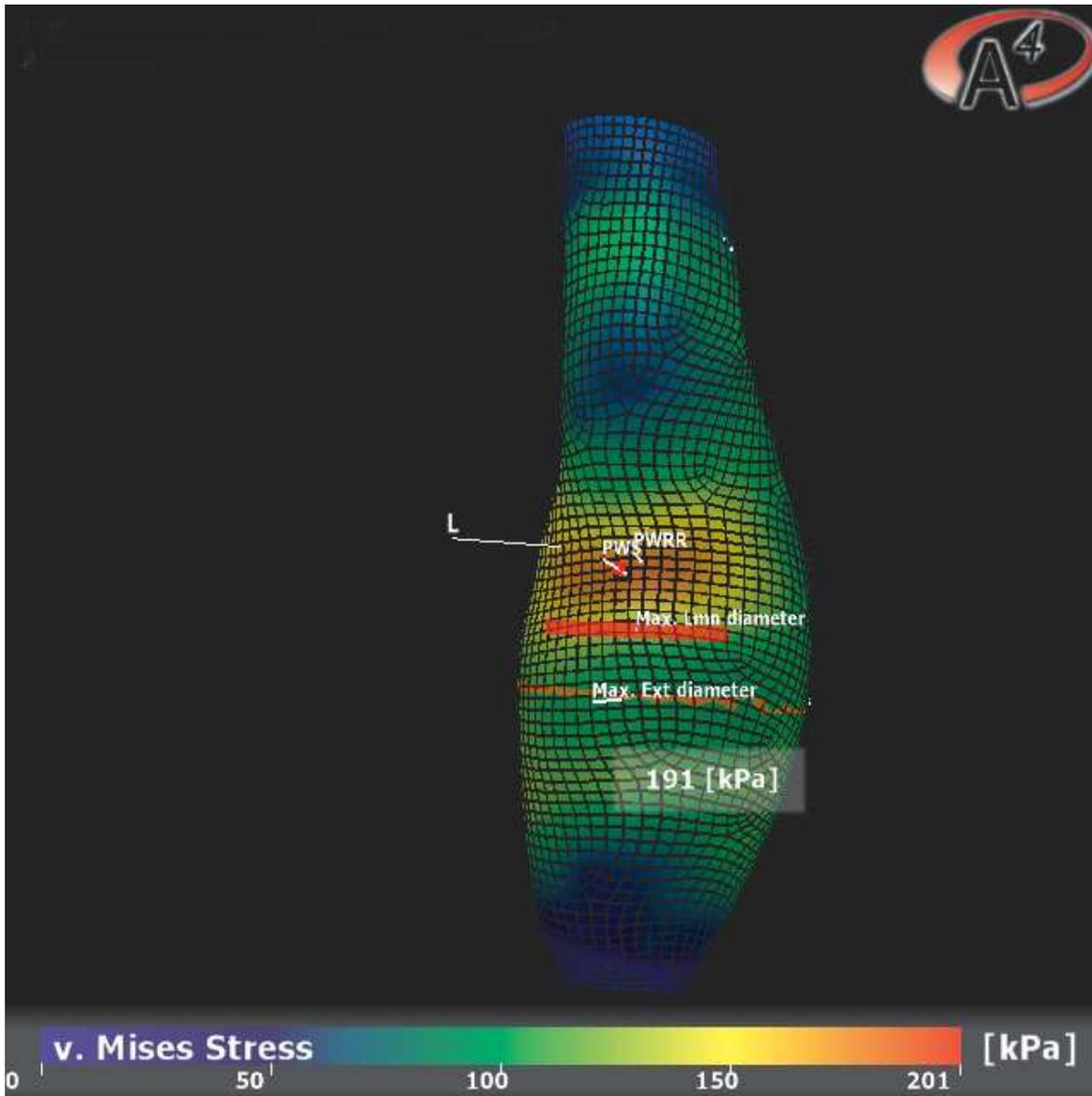
Venkatasubramaniam *et al.* has been abbreviated to 'Subramaniam' due to space constraints. Study-specific estimates were combined using inverse-variance (IV) weighted average of logarithmic SMDs in a random-effects model.

Table 1: Comparison of PWS in asymptomatic intact and symptomatic or ruptured AAAs

Study	Total N	Asymptomatic intact AAAs		Symptomatic or ruptured AAAs		p-value†
		N	PWS (N/cm ²)	N	PWS (N/cm ²)	
Measured at population systolic blood pressure						
Fillinger, 2002, Lebanon ^{18 #}	40	30	36.9±8.8	10	47.7±20.6	0.024
Fillinger, 2003, Lebanon ^{22 #}	61	39	42.0±12.5	22	58.0±18.8	<0.001
Venkatasubramanium, 2004, UK ^{24 *}	27	15	62.0±28.0	12	102.0±38.0	0.004
Vande Geest, 2006, USA ^{21 #}	13	5	46.0 ±9.6	8	49.9±11.3	0.537
Truijers, 2007, USA ^{23 #}	20	10	39.7±10.4	10	51.7±7.6	0.009
Heng, 2008, UK ^{20 *}	70	40	67.0±30.0	30	111.0±51.0	<0.001
Vande Geest, 2008, USA ^{25 #}	14	5	46.0±9.5	9	49.9±12.1	0.546
Maier, 2010, Germany ^{19 **}	53	30	34.3±10.5	23	47.7±12.5	<0.001
Gasser, 2010, Sweden ^{26 **}	50	30	27.6±11.7	20	35.2±12.6	0.034
Measured at standardised systolic blood pressure (120 mmHg)						
Fillinger, 2002, Lebanon ^{18 #}	40	30	32.2±7.7	10	38.0±9.5	0.058
Fillinger, 2003, Lebanon ^{22 #}	61	39	37.0±12.5	22	46.0±14.1	0.012
Venkatasubramanium, 2004, UK ^{24 *}	27	15	55.0±24.0	12	77.0±29.0	0.041
Truijers, 2007, USA ^{23 #}	20	10	31.7±7.3	10	36.7±12.7	0.293
Heng, 2008, UK ^{20 *}	70	40	65.0±25.0	30	84.0±31.0	0.006

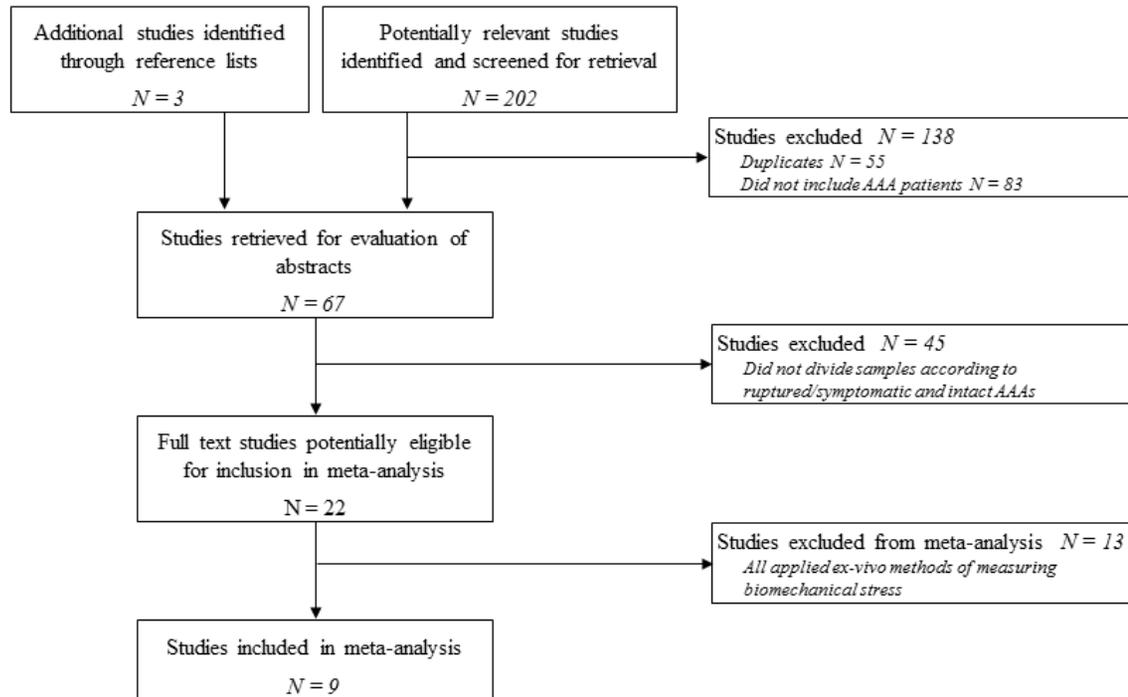
PWS is reported as mean ± standard deviation; † p-values for t-test comparisons between asymptomatic and ruptured AAA calculated by RevMan 5.2 based on data extracted from assessed papers; *PWS was converted from Megapascals (MPa) to N/cm²; ** PWS was converted from Kilopascals (kPa) to N/cm²; # PWS values converted from standard error to standard deviation.

Figure 1



This is the accepted version of a paper published in the *British Journal of Surgery* (DOI: 10.1002/bjs.9578). At the time of submission to JCU Research Online this paper is still awaiting official citation information from the publishers.

Figure 2



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Figure 3

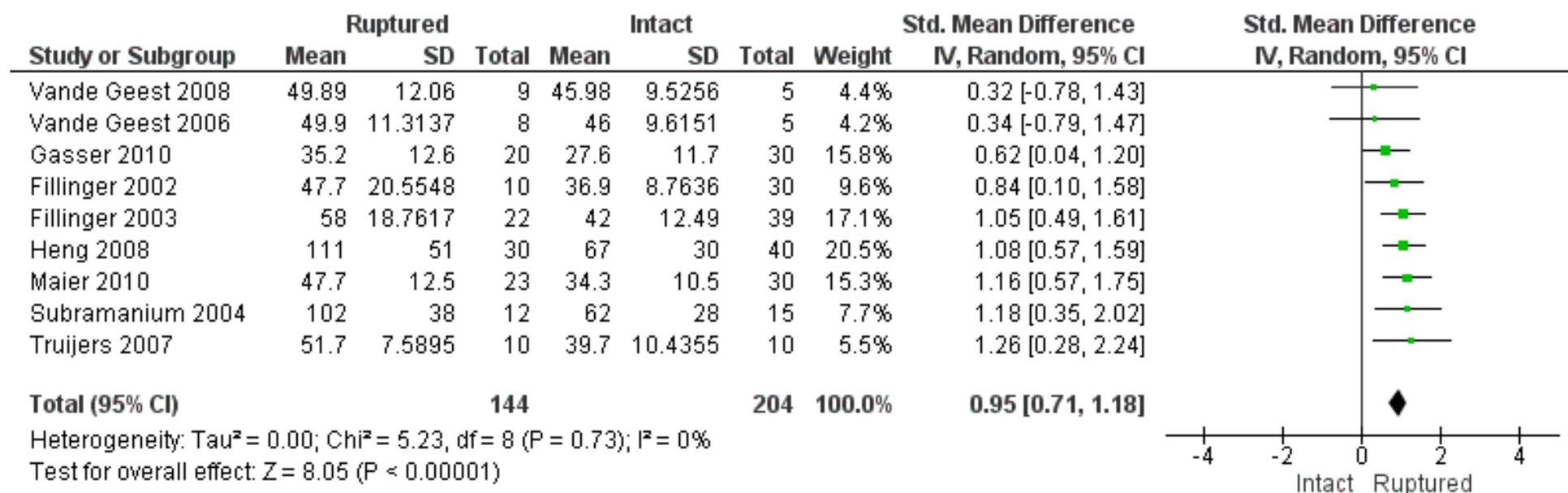
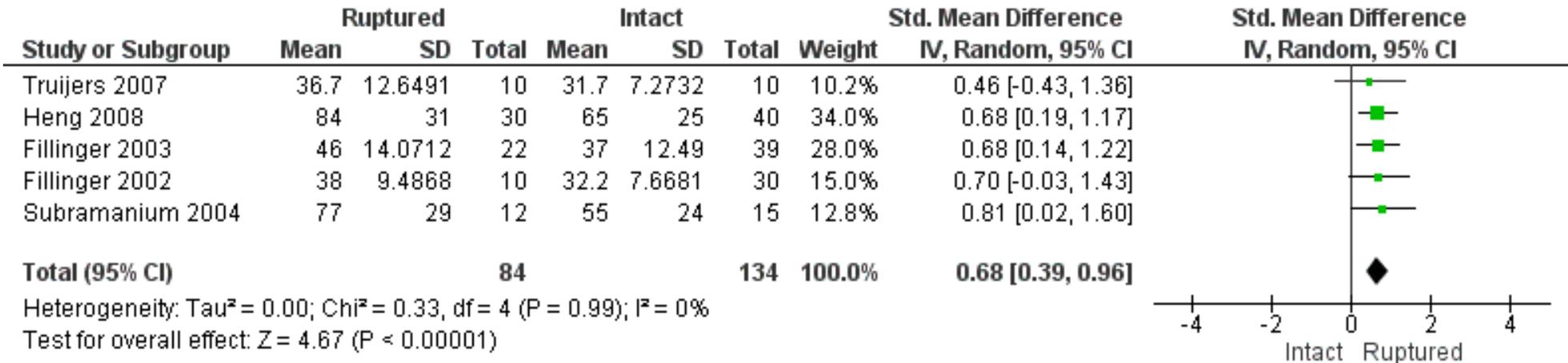


Figure 4



Supplementary Table 1

Studies	Fillinger 2002, ¹⁸ Lebanon		Fillinger 2003, ²² Lebanon		Venkatasubramaniam 2004, ²⁴ UK		Vande Geest 2006, ²¹ USA		Truijers 2007, ²³ USA		Heng 2008, ²⁰ UK		Vande Geest 2008, ²⁵ USA		Maier 2010, ¹⁹ Germany		Gasser 2010, ²⁶ Sweden	
	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Control s	Cases	Controls	Cases	Controls	Cases
Study quality	Good		Good		Fair		Poor		Fair		Fair		Poor		Fair		Good	
number	30	R=10 [^]	39	S/R=22	15	R=12	5	R=8	10	R=10	40	S/R=30	5	R=9	30	S/R=23	30	R=20
Average age of patients (in years)	69±3**	76±3**	72±1**	75±2**	75 (66-90)***	75 (71-84)***	n/a	n/a	72±2**	70±2**	76 (60-89)****	74 (60-89)****	n/a	n/a	68.8±7.4*	77.0±9.5*	76±8.5*	77±10.8*
Average maximal AAA diameter (in mms)	61±2**	69±5**	59±1**	61±2**	68±15.2*	76±4.5*	61±5**	68±3**	51±2**	53±2**	65±13.0*	70±13.9*	n/a	n/a	56.4±11.0*	75.1±16.8*	70.2±22.7*	81.1±20.2*
% Female	10	30	21	41	16.7	16.7	n/a	n/a	10	30	27.8	20.0	n/a	n/a	20	39	13.3	20
% Smokers	87	90	21	36	33	57	n/a	n/a	40	40	62	78	n/a	n/a	n/a	n/a	n/a	n/a
Average maximal arterial blood pressure (mmHg)	131±2**	142±11*	134±2**	150±6*	n/a	n/a	n/a	n/a	147±5**	165±7*	143±25*	151±23*	n/a	n/a	n/a	n/a	151.2±25.6*	144.8±26.4*
% History of Coronary heart disease	63	40	69	47	33	50	n/a	n/a	70	30	24	50	n/a	n/a	n/a	n/a	n/a	n/a

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Supplementary Table 1 continued – Footnote information

AAA= Abdominal aortic aneurysm; CVD= Cardiovascular disease; Controls had asymptomatic intact AAAs; Cases included symptomatic or ruptured AAAs; S= Symptomatic AAAs; R= Ruptured AAAs; n/a= Data was unavailable. The assessment of study quality is described in the methods section.

* Mean and standard deviation

** Mean and standard error

*** Median and range within brackets

**** Median and interquartile range within brackets

^ Symptomatic patients (n= 8) were excluded from this study.

Supplementary Table 2: Leave-one-out sensitivity analyses of the included studies.

Study omitted	Standard Mean Difference (MD)	95% Confidence Interval	p value
Fillinger 2002, Lebanon	0.96	0.71, 1.20	<0.001
Fillinger, 2003, Lebanon	0.92	0.67, 1.18	<0.001
Venkatasubramanium, 2004, UK	0.93	0.69, 1.16	<0.001
Geest, 2006, USA	0.97	0.74, 1.21	<0.001
Truijers, 2007, USA	0.93	0.69, 1.16	<0.001
Geest, 2008, USA	0.97	0.74, 1.21	<0.001
Heng, 2008, USA	0.91	0.65, 1.17	<0.001
Maier, 2010, Germany	0.91	0.66, 1.16	<0.001
Gasser, 2010, Sweden	1.01	0.76, 1.26	<0.001