Supplemental Material

Data S1.

Protocol for the systematic review and meta-analysis

Protocol for a systematic review and meta-analysis of peak wall stress and peak wall rupture index in ruptured and asymptomatic intact abdominal aortic aneurysms.

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Background: Aortic peak wall stress (PWS) and peak wall rupture index (PWRI) are established surrogate measures of abdominal aortic aneurysm (AAA) rupture risk. Prior studies have suggested that PWS and PWRI is greater in ruptured than asymptomatic intact AAAs, although it remains unclear whether these measures confer any benefit in predicting AAA rupture compared to AAA diameter. The aim of this planned systematic review and meta-analysis is to compare PWS and PWRI in participants with ruptured and asymptomatic intact AAAs of similar diameter.

Methods: A systematic review and meta-analysis will be conducted. An electronic database search will be performed using predefined search terms to identify relevant studies. Eligible studies will be required to compare PWS and PWRI in ruptured and asymptomatic intact AAAs of similar diameter. Random-effects meta-analysis will be performed and leave-one-out sensitivity analyses will be conducted to assess the robustness of the findings. Risk of bias will be assessed using a modification of the Newcastle-Ottawa scale and standard quality assessment criteria for evaluating primary research papers.

Discussion: This meta-analysis will be the first to compare PWS and PWRI in asymptomatic intact and ruptured AAAs of similar diameter.

Introduction

Abdominal aortic aneurysm (AAA) rupture is an important cause of mortality.[1] In current clinical practice, AAA aortic diameter is the main measure used by clinicians to estimate the

risk of AAA rupture.[1, 5] Evidence from prior randomized controlled trials suggest that some large AAAs remain stable throughout a patient's lifetime, while some small AAAs can rupture.[2] This suggests that diameter is not a perfect measure of estimating the rupture risk of AAAs.[1, 5] There has been considerable interest in utilizing biomechanical measures to estimate and predict AAA rupture risk.[3, 7] Aortic peak wall stress (PWS) and peak wall rupture index (PWRI) are examples of two widely reported biomechanical indices.[7, 26] Prior meta-analyses have suggested that PWS is greater in asymptomatic intact and ruptured AAAs although the diameter in both groups were different in that analysis.[3] A meta-analysis comparing PWRI in asymptomatic intact and ruptured AAAs in individuals with similar aortic diameter has not been performed. In light of the limitations of prior studies and the paucity of pooled evidence in this area an updated systematic review and meta-analysis is required.

Systematic review question

Is PWS and PWRI greater in asymptomatic intact and ruptured AAAs of similar aortic diameter ?

Data sources search terms and search strategy

This literature review will be performed using the Web of Science (via ISI Web of Knowledge; 1965), Scopus (1966), Medline (via OvidSP, 1966) and The Cochrane Library. A combination of the following search terms will be used: "peak wall stress" OR "peak wall rupture index" OR "rupture potential index" AND "abdominal aortic aneurysm". Specific search criteria database are reported below:

Medline (via OvidSP, 1966): ((peak wall stress) OR (peak wall rupture index)) AND (abdominal aortic aneurysm) [Across all fields]

Web of Science (via ISI Web of Knowledge; 1965): (((peak wall stress) OR (peak wall rupture index)) AND (abdominal aortic aneurysm)) Timespan: All years. Indexes: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI, CCR-EXPANDED, IC.

Scopus (1966): TITLE-ABS-KEY (((peak AND wall AND stress) OR (peak AND wall AND rupture AND index)) AND (abdominal AND aortic AND aneurysm))

The Cochrane Library: peak wall stress in All Text OR peak wall rupture index in Title Abstract Keyword AND abdominal aortic aneurysm in Title Abstract Keyword - (Word variations have been searched)

Inclusion and exclusion criteria

Case-control studies investigating PWS in patients with ruptured and diameter matched asymptomatic intact AAAs. Eligible studies should be of case-control design. The AAA diameter between asymptomatic intact and ruptured groups should be similar (within 3mm mean difference). Studies that include symptomatic AAA patients in the ruptured group will be excluded. To avoid double-counting of data, the study population in a given publication should not have been used in a previous study of those included in the review.

Data extraction (selection and coding)

Data will be extracted by three authors independently (TS, JM and JG). The following data will be collected: Sample sizes for the ruptured and asymptomatic intact AAA group, study design, software used to perform finite element analysis (FEA), PWS and PWRI estimates, AAA diameter, risk factors (including age, sex, smoking history, hypertension, diabetes, ischaemic heart disease [IHD], stroke, chronic obstructive pulmonary disease [COPD]) and systolic blood pressure. If relevant data is not reported in the publication, the corresponding will be contacted via email.

Assessment of methodological quality (risk of bias)

A quality assessment tool has been created to assess the risk of bias of the included studies. This tool was created by the authors and incorporates components of two widely reported quality assessment tools (Newcastle-Ottawa scale and Standard quality assessment criteria for evaluating primary research papers).[13, 14] A number of additional criteria relevant to this systematic review will also be included. This includes: criteria used to define AAA rupture; reporting of the method used to estimate PWS and PWRI and reproducibility; use of a standardised blood pressure in PWS and PWRI calculations (i.e. use of a single blood pressure measurement for all participants or omission of blood pressure in calculations); inclusion of CT scan prior to or after rupture (for ruptured cases); matching for AAA diameter between asymptomatic intact and ruptured cases; matching for other confounding variables. The overall risk of bias assessed within each study will be assessed as low, medium or high based on predefined criteria. Please see Supplementary Table 1 for further details regarding the quality assessment tool.

Approach to meta-analysis

Meta-analyses will be performed using inverse variance-weighted methods.[15] Standardised mean differences (SMD) with 95% confidence intervals (CI) will be calculated for both PWS and PWRI pooled estimates. Previous meta-analyses have identified there is no standardised method of computing PWS and PWRI and therefore SMDs will be calculated using random-effects weighting to account for likely inter-study methodological heterogeneity.[17] PWS outcome data will be converted from Newton Per Square Centimeter (N/cm^2) to kilopascal (kPa) where required to ensure that units are consistent for the meta-analysis.[16] Inter-study heterogeneity will be assessed using the I^2 index and values <25%, between 25-75% and >75% will be considered to represent low, moderate and high heterogeneity, respectively.[17] If PWS and PWRI are computed at a standardised blood pressure (i.e single blood pressure for

all participants) this value will be used in the meta-analysis. If a standardised blood pressure is not used, PWS and PWRI calculated at patient specific blood pressures will be used. To identify sources of heterogeneity a leave-one-out-sensitivity analysis will be planned. This will involve excluding individual studies one at a time and recalculating the pooled estimates for the remaining studies. Publication bias will be assessed by funnel plots comparing the summary estimate of each study to its precision (1/standard error) for outcomes that are reported in ≥5 studies.[21] Analyses will be conducted using Stata version 16.1 (StataCorp LP, College Station, Texas, USA). All statistical tests will be two-sided and a p-value of <0.05 will be considered significant.

Ethics and dissemination

Ethical approval is not required for this systematic review and meta-analysis as data already available in scientific databases will be analysed. The results of this review will be submitted for peer-reviewed publication and findings will be presented at conferences.

Table S1. Criteria used to perform the assessment of methodological quality.

Category	Criteria	Response		
		Yes	Partial	No
Clearly defined objective?	Clear hypothesis stated and tested. Objective easily identified in introductory section (or first paragraph of methods section). • Specifies all the following: purpose, subjects/target population, and the specific association(s)/descriptive parameter(s) under the investigation.	X		
	Vaguely/incompletely reported (e.g. "describe the effect of" or "examine the role of") OR substantial information must be collected from parts of the paper other than introduction/background/objective section.		X	
	Question or objective is not reported or is incomprehensible.			X
Prospective study design?	Hypothesis designed prior to selection of participants.	X		
	• Hypothesis and selection criteria designed after the occurrence of respective endpoints (e.g. AAA rupture). • Data collection conducted retrospectively after participants experienced outcomes of interest (e.g AAA rupture)			X
Selection criteria well described?	Selection strategy designed to obtain an unbiased sample of the relevant target population. • Methods for selection/recruitment/sampling reported in the study. • Definition of AAA adequately described (appropriate investigations used including ultrasound, angiography, or clinical assessment by a vascular specialist, or scheduled surgical repair of AAA etc.)	X		

|				
	• At least 3 of the specified exclusion criteria described [listed below]			
	Selection methods (and inclusion/exclusion criteria) are not completely described OR selection methods described elsewhere. • Included patients who have either an intact OR ruptured AAA AND no previous endovascular or open surgical repair • Available CT scan of non-ruptured AAA OR • Available CT scan of ruptured AAA at the time of rupture prior to any surgical intervention. • Excluded patients where there was no CT scan of the AAA available for analysis. • Excluded patients where poor quality of CT scans or technical factors (e.g. extreme vessel wall angulation; contrast extravasation) precluded PWS/PWRI estimation.		X	
	No information provided; OR obviously inappropriate selection procedures.			X
Was an objective definition of AAA rupture utilised?	Appropriate definition of AAA rupture used including both of the following criteria: • Diagnosis of a ruptured AAA by a consultant vascular physician/surgeon • AAA associated with objective evidence of blood within the peritoneum identified on a CT scan or alternate imaging modality	X		
	Limited definition of ruptured AAA described: • Definition restricted to diagnosis by consultant vascular physician/surgeon OR • Definition restricted to diagnosis on imaging, but no description of radiological findings to support diagnosis of ruptured AAA • AAA rupture diagnosis based on electronic coding		X	

	No definition of ruptured AAA described			X
Assessment of outcome – Method of estimating PWS and PWRI well described	Method of estimating PWS and PWRI well described and: • Reproducibility evaluated and reported within paper AND • Reproducibility determined to be moderate-high	X		
	Method of estimating ILT well described: • no assessment of reproducibility reported OR • Reproducibility determined to be low		X	
	Method of estimating ILT not described OR limited description provided AND no assessment of reproducibility made			X
Standardised blood pressure used for PWS/PWRI measurements?	A standard blood pressure (e.g 140/80 mmHg) was used to compute PWS and PWRI measurements for all patients	X		
	Patient specific blood pressure (at the time of CT scan) was used to perform PWS/PWRI measurements			X
Sample size calculation/estimation reported in methodology.	Details of sample size calculation/estimation reported in methodology	X		
	Required sample size reported, but no details on how this was calculated/estimated		X	
	No sample size calculation/estimation conducted			X
What was the sample size?	<50 OR 50-100 OR >100	N/A	N/A	N/A
	Not reported	N/A	N/A	N/A

Did participants with AAA rupture undergo a CT scan prior rupture and after rupture	For all patients, CT data were present both before and during the rupture event.	X		
				X
Were participant characteristics adequately described?	Sufficient relevant baseline information clearly characterising the participants are provided (or reference to previously published baseline data is provided). Includes at least 5 of the following: • Age, Gender, AAA diameter (mm), smoking, HTN, diabetes, coronary artery disease, statin prescription, aspirin prescription.	X		
	Poorly defined criteria or incomplete relevant baseline / demographic information (e.g. Information on likely confounders not reported). • Includes less than 5 of the characteristics reported above.		X	
	No baseline / demographic information provided.			X
Were participants in the ruptured and intact AAA groups matched for diameter?	To provide an objective comparison of ruptured and intact AAAs, both groups were matched for maximum diameter.	X		
				X
Was participants matched for other confounding factors for AAA rupture?	Matching undertaken or adjustments are made for at least 2 of the following variables: • Age, sex, HTN, smoking and diabetes	X		
	Did not meet the criteria above OR did not specify which variables were adjusted or matched for		X	

|	No adjustment or matching undertaken for confounding factors other than maximum diameter			X

Overall risk of bias within study	Criteria
Low	>10 criteria with 'Yes' response and sample size > 100
Medium	>5 and ≤10 criteria with 'Yes' response and sample size between 50-100
High	≤5 criteria 'Yes' response and sample size between <50 or between 50-100.

Figure S1. Leave-one-out sensitivity analysis for the meta-analysis of PWS in asymptomatic intact and ruptured AAAs.
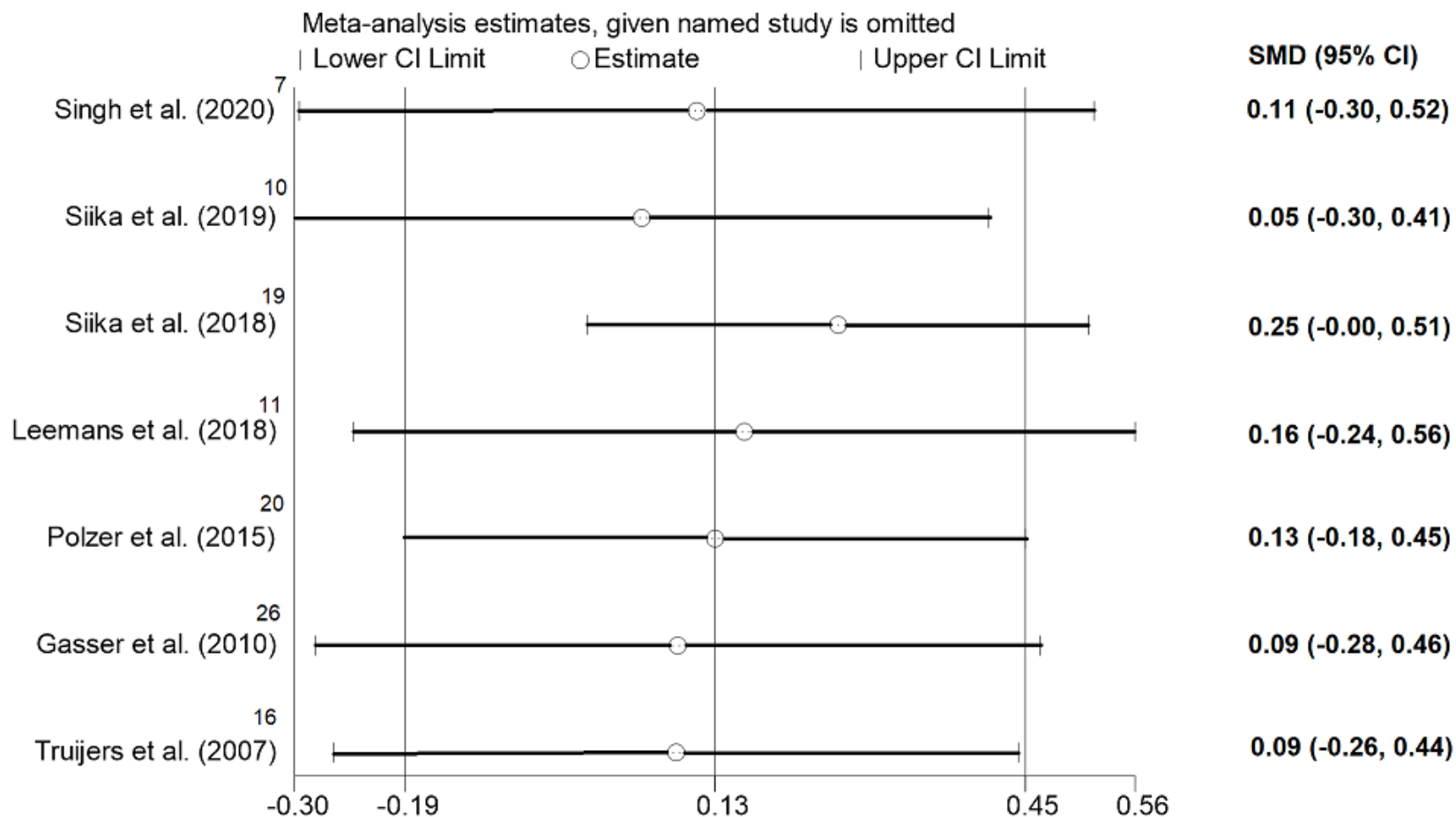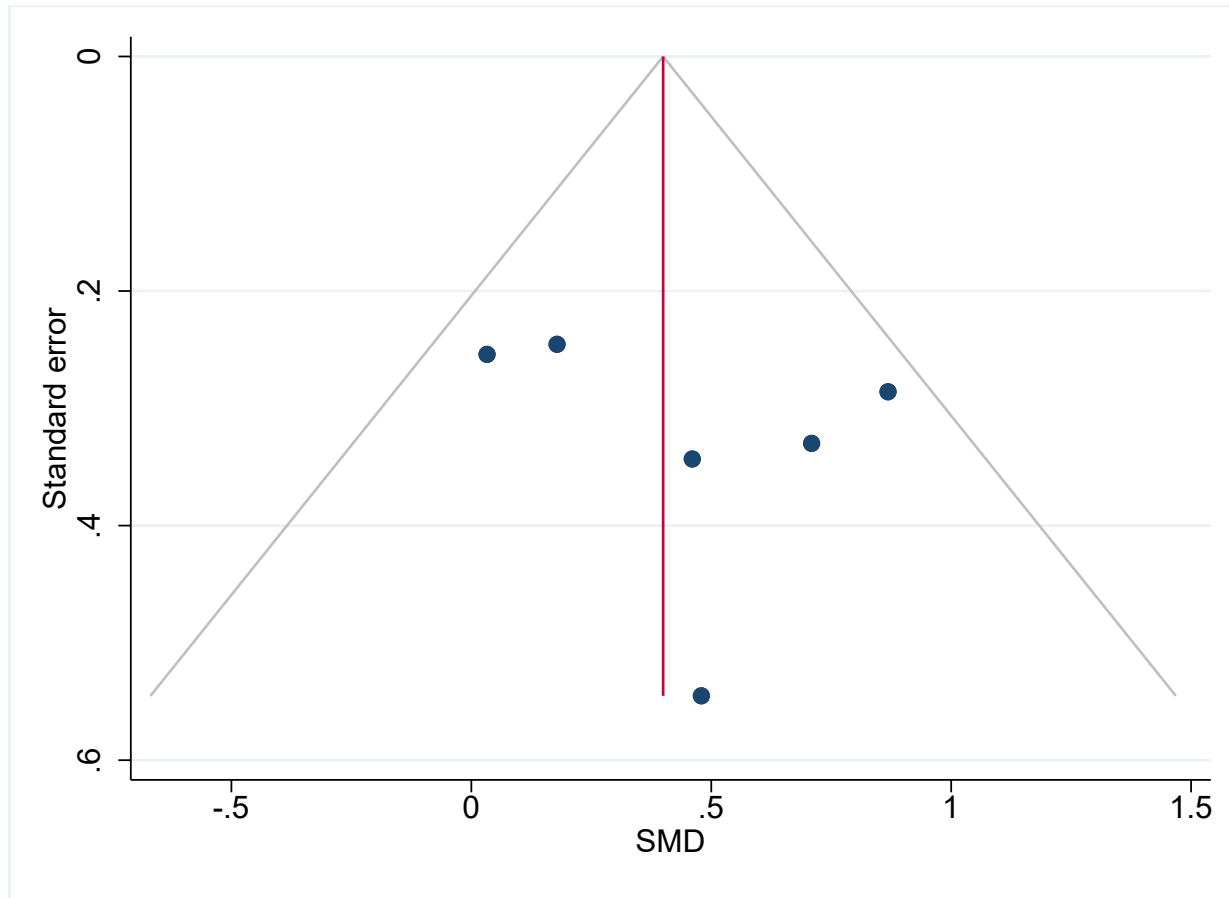

SMD, standardised mean difference; CI, confidence intervals. Indicates the pooled results with the corresponding study excluded from the analysis.

Figure S2. Leave-one-out sensitivity analysis for the meta-analysis of PWRI in asymptomatic intact and ruptured AAAs.
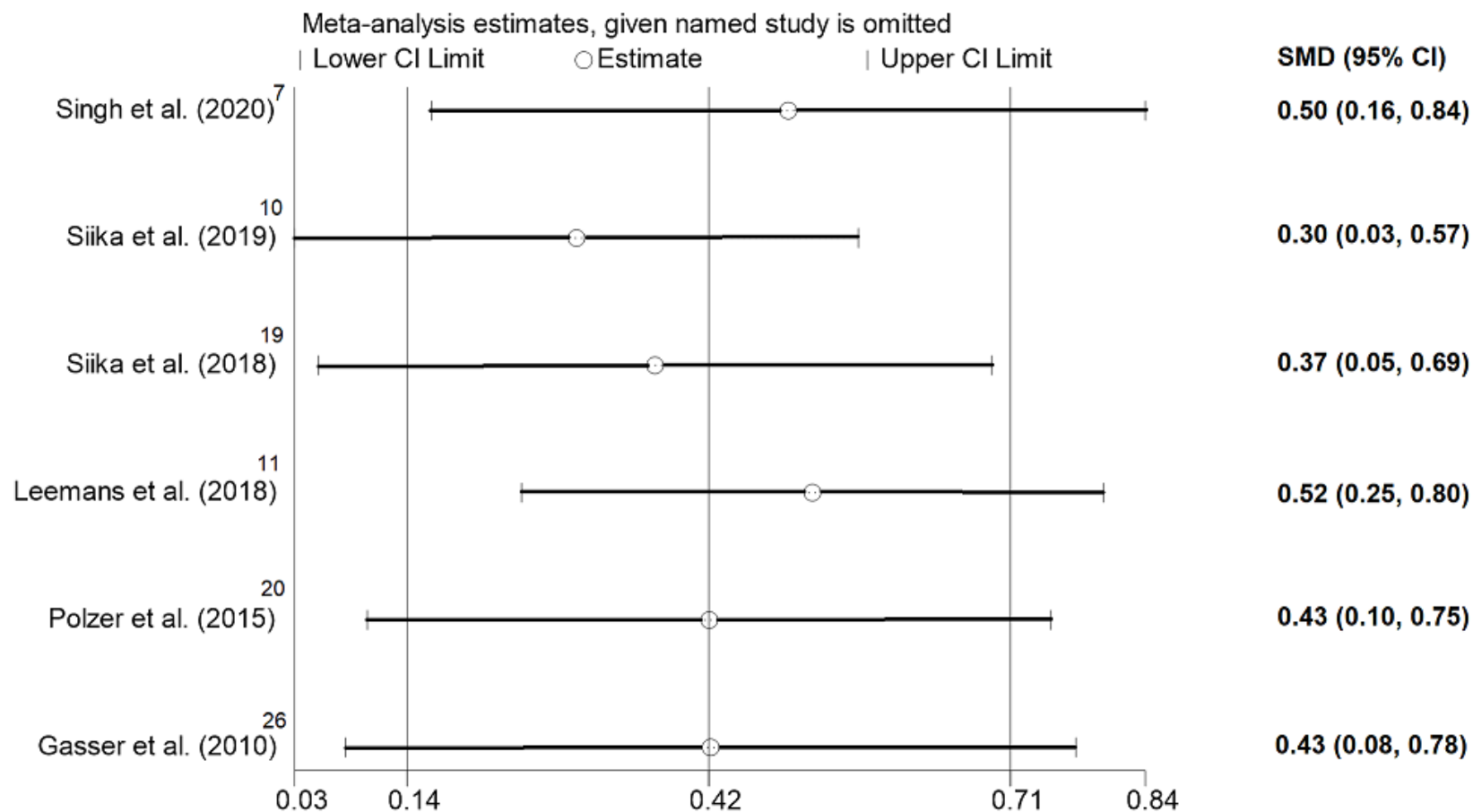
SMD, standardised mean difference; CI, confidence intervals. Indicates the pooled results with the corresponding study excluded from the analysis.

Figure S3. Funnel plot with pseudo 95% CIs of the difference in PWRI between ruptured and asymptomatic intact AAAs.

SMD, standardised mean difference; PWRI, peak wall rupture index; CI, confidence intervals.