

## SYSTEMATIC REVIEW AND META-ANALYSIS

# Synchronous and Metachronous Thoracic Aortic Aneurysms in Patients With Abdominal Aortic Aneurysms: A Systematic Review and Meta-Analysis

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**BACKGROUND:** The prevalence of thoracic aortic aneurysms (TAA) in patients with known abdominal aortic aneurysms (AAA) is not well known and understudied. Our aim was to conduct a systematic review and meta-analysis of the overall prevalence of synchronous and metachronous TAA (SM-TAA) in patients with a known AAA and to understand the characteristics of this sub-population.

**METHODS AND RESULTS:** We searched MEDLINE, EMBASE, and CENTRAL (Cochrane Central Register of Controlled Trials) from inception to November 2019 for all population-based studies reporting on the prevalence of SM-TAAs in a cohort of patients with AAA. Article screening and data extraction were performed by 2 authors and data were pooled using a random-effects model of proportions using Freeman-Tukey double arcsine transformation. The main outcome was the prevalence of SM-TAAs in patients with AAAs. Secondary outcomes were the prevalence of synchronous TAAs, metachronous TAAs, prevalence of TAAs in patients with AAA according to the anatomic location (ascending, arch, and descending) and the differences in prevalence of these aneurysms according to sex and risk factors. Six studies were included. The pooled-prevalence of SM-TAA in AAA patients was 19.2% (95% CI, 12.3–27.3). Results revealed that 15.2% (95% CI, 7.1–25.6) of men and 30.7% (95% CI, 25.2–36.5) of women with AAA had an SM-TAA. Women with AAA had a 2-fold increased risk of having an SM-TAA than men (relative risk [RRs], 2.16; 95% CI, 1.32–3.55). Diabetes mellitus was associated with a 43% decreased risk of having SM-TAA (RRs, 0.57; 95% CI, 0.41–0.80).

**CONCLUSIONS:** Since a fifth of AAA patients will have an SM-TAA, routine screening of SM-TAA and their clinical impact should be more thoroughly studied in patients with known AAA.

**Key Words:** abdominal aortic aneurysms ■ meta-analysis ■ metachronous aortic aneurysms ■ synchronous aortic aneurysms ■ thoracic aortic aneurysms

**A**neurysmal disease is known nowadays to be a systemic, multifactorial, and unpredictable condition with different causes, behaviors and presentations which increase the complexity of its diagnosis, treatment, and outcomes.<sup>1,2</sup>

Abdominal aortic aneurysms (AAA) are by far the most common and studied aneurysms and screening

strategies have shown to be effective, reducing the incidence in aneurysm rupture rate and improvement of care in a cost-effective fashion.<sup>3</sup>

The presence of synchronous and metachronous aneurysms has been well described in the literature.<sup>4</sup> However, in contrast to synchronous peripheral aneurysms which are frequently screened and reported,

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## CLINICAL PERSPECTIVE

### What Is New?

- We found that 19.2% of patients with abdominal aortic aneurysm have a synchronous or metachronous thoracic aortic aneurysm.
- Women have a 2-fold higher risk of having a synchronous or metachronous abdominal and thoracic aortic aneurysm.
- Diabetes mellitus is associated with a 43% decreased risk of having a synchronous or metachronous abdominal and thoracic aortic aneurysm.

### What Are the Clinical Implications?

- Routine screening of synchronous/metachronous thoracic aortic aneurysms and their clinical impact should be more thoroughly studied in patients with known abdominal aortic aneurysms.
- Differences in prevalence found between men and women might explain, in part, why women have worse outcomes following abdominal aortic aneurysm repair.

## Nonstandard Abbreviations and Acronyms

<b>CENTRAL</b>	Cochrane Central Register of Controlled Trials
<b>SM-TAA</b>	synchronous and metachronous thoracic aortic aneurysms
<b>TAA</b>	thoracic aortic aneurysms

the incidence and behavior of synchronous/metachronous thoracic aortic aneurysms (SM-TAA) is underappreciated.<sup>4</sup>

In a previous study in our center, we found that 18.9% of patients submitted to Thoracic Endovascular Aortic Repair, had a synchronous or metachronous AAA.<sup>5</sup> However, thoracic aortic aneurysms (TAA) in general, do not have a screening program to date and the incidence and prevalence of these aneurysms is underappreciated. Since rupture of TAAs in patients with a known AAA or following an AAA repair has been described,<sup>4,6,7</sup> better understanding of the prevalence of these synchronous/metachronous TAAs in patients with a known AAA might be crucial for patients, physicians, and policy makers.

Our aim was to estimate the overall prevalence of synchronous and metachronous TAAs in patients with a known AAA.

## METHODS

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines<sup>8</sup> were followed for reporting and design of this systematic review. The authors declare that all supporting data are available within the article (and its online supplementary files).

### Eligibility Criteria

We included all cohort studies, either prospective or retrospective, reporting on the prevalence of thoracic aortic aneurysms in a population of patients with known abdominal aortic aneurysm, irrespective of the diagnostic method used. We accepted the definition of AAA or TAA provided by the studies. We defined synchronous aneurysms as occurring concomitantly and metachronous aneurysms if the diagnosis of a new TAA occurred 2 years after the initial AAA diagnosis and no TAA was present initially.

There were no date or language restrictions. Animal studies were not included.

Papers were excluded if they did not specify the specific number of SM-TAA. If the same population was described in 2 papers 1 of them was excluded to not duplicate events. Papers were also excluded if the studied population (the denominator) included patients without AAA.

### Information Sources and Search Method

We searched EMBASE, MEDLINE, and CENTRAL (Cochrane Central Register of Controlled Trials), from inception to November 2019. We also cross-checked references and consulted specialists for additional potential studies. The search strategy is detailed in Table S1.

The search results were cross-checked, and duplicates were eliminated.

### Study Selection, Data Collection Process, and Synthesis

Two authors (R.G.M. and A.L.) independently screened the titles and abstracts that yielded from the search. Full-text papers were also independently assessed by both authors and disagreements were resolved by consulting with a third author (G.D.).

After the final search result, data were independently extracted by 2 authors (R.G.M. and A.L.) using a pre-design report form and uploaded onto a table sheet after cross-checking.

Data retrieved included: study publication data (authors, date, journal), population studied (years of the study and respective centers), study site, number of participants with known AAA, number of patients with SM-TAA and AAA, demographics (age, sex, risk

factors), location of the TAA, diagnostic methods used, and definitions of TAA and AAA used.

The main outcome of interest was the overall prevalence of SM-TAA in patients with known AAA. The prevalence was defined as the number of existing TAAs at the time of the study in the population of patients with known AAA.

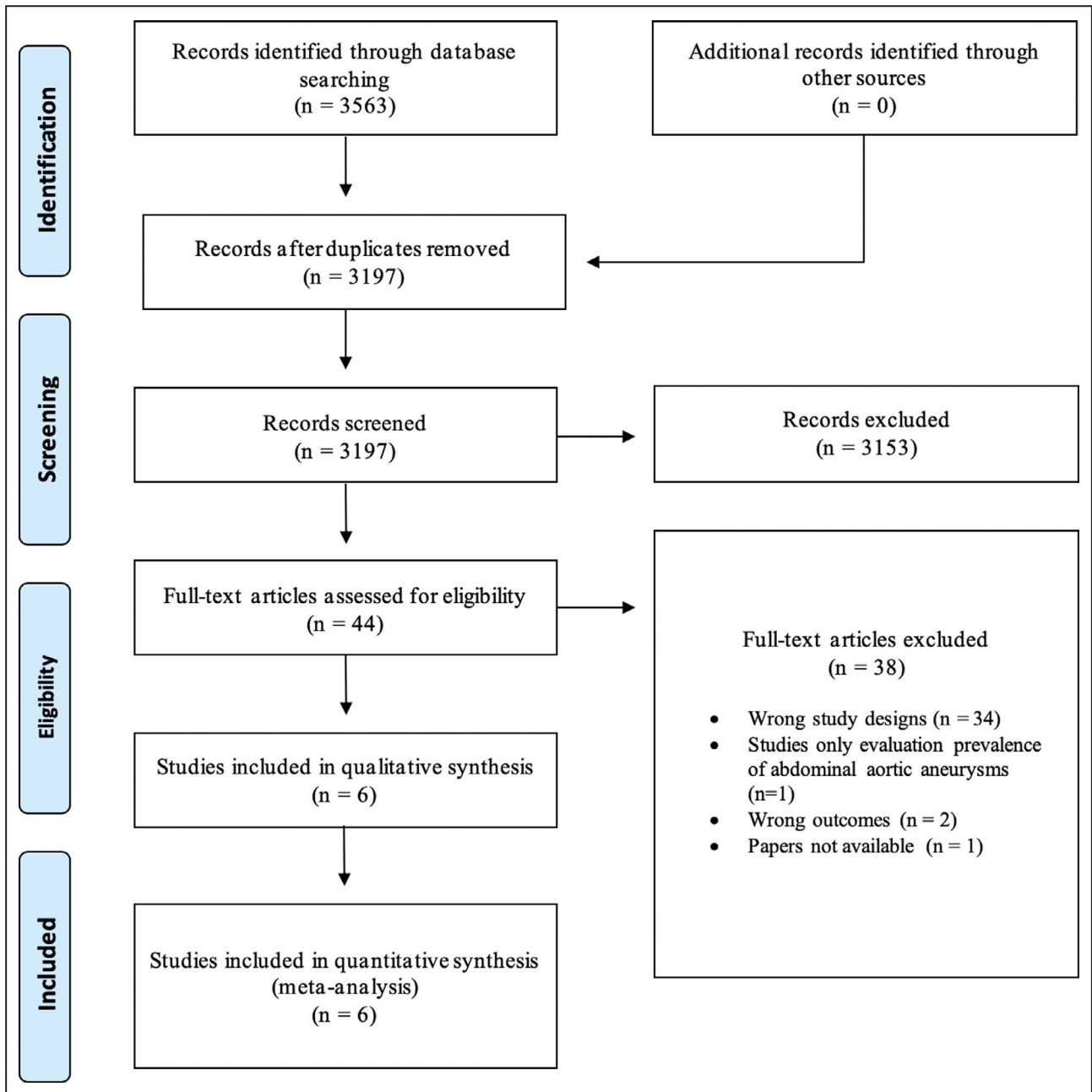
The secondary outcomes of interest included the prevalence of synchronous TAAs; the prevalence of metachronous TAAs; the prevalence of SM-TAA according to the anatomic location and the difference in the prevalence of SM-TAA and AAA according to sex and other risk factors (smoking, hypertension, diabetes

mellitus, family history of AAA/TAA, hyperlipidemia, and chronic obstructive pulmonary disease).

### Statistical Analysis

We used the Open-Meta (Analyst) Software<sup>9</sup> for quantitative analysis and to derive forest plots, when appropriate.

The results yielded by the data extraction were expressed in percentages for the prevalence of SM-TAA. The total number of individuals with known AAA was used as the denominator and the number of patients with SM-TAA and AAA as the numerator.



**Figure 1.** Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram.

**Table 1. Study Details Including Cohort Origin and Definitions**

Study	Years of the Study	Location	Cohort Origin	Definition of AAA	Definition of TAA	Methods of Diagnosing TAA
Larsson et al, 2011 <sup>15</sup>	2004–2008	Stockholm, Sweden (Karolinska University Hospital)	Patients with AAA diagnosis attending the outpatient clinic	Diameter $\geq 30$ mm	Women: AAD $>42$ mm, DAD $>33$ mm; Men: AAD $>47$ mm and DAD $>37$ mm	CT
Chaer et al, 2012 <sup>4</sup>	2000–2008	Pittsburgh, Pennsylvania, USA (University of Pittsburgh)	Electronic medical record	Diameter $>50\%$ normal diameter or diameter $\geq 30$ mm	Diameter $>30$ mm	CT, MR, or MR angiogram
Takigawa et al, 2012 <sup>18</sup>	2001–2006	Yokosuba, Japan (Cardiovascular Center)	Undergoing elective graft replacement for asymptomatic infrarenal AAA	NR	Diameter $>40$ mm	CT
Agricola et al, 2013 <sup>14</sup>	2013	Milan, Italy (San Raffaele Hospital)	Patients with AAA who underwent TE before surgery	NR	Women: AAD $>42$ mm, AArchD $>32$ ; Men: AAD $>47$ mm, AArchD $>37$ mm	TE
Wallinder et al, 2018 <sup>17</sup>	2013	Uppsala and Västernorrland, Sweden	Swedish national vascular registry	Diameter $\geq 30$ mm	Diameter $\geq 42$ (ascending); D $\geq 33$ (descending)	CT
Dombrowski et al, 2019 <sup>16</sup>	2007–2017	Michigan, USA (Beaumont Health System)	Radiology reports of AAA	Diameter $\geq 30$ mm	Diameter $\geq 40$ mm	CT

AAA indicates abdominal aortic aneurysms; AAD, ascending aortic diameter; AArchD, aortic arch diameter; CT, computed tomography; DAD, descending aortic diameter; MR, magnetic resonance; NR, not reported; TAA, thoracic aortic aneurysm; and TE, transthoracic echocardiography.

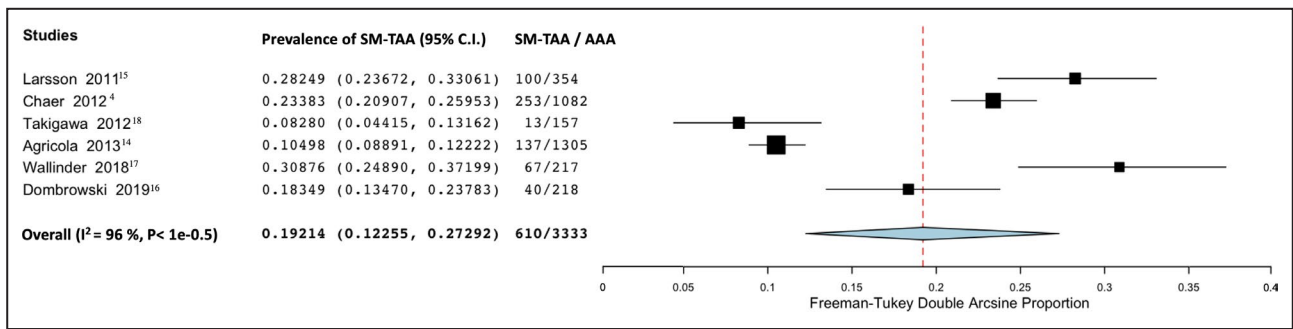
A random-effects model was used to pool the data to account for the heterogeneity of the included studies.<sup>9</sup> The random-effects model of DerSimonian and Laird was used by default as this approach is the simplest and most commonly used method for fitting the random effects model and is particularly useful for larger samples.<sup>10</sup> Freeman-Tukey transformation (double arcsine transformation) was used to adjust the data set to estimate the frequency of the events, limiting the

CI among 0% to 100%.<sup>11</sup> For subgroup sex analysis, we dichotomized the prevalence data and used male sex as the reference group and for subgroup risk factor analysis we used the group with AAA-only as the reference group, results were reported using risk ratios [RRs] and 95% CIs. Statistical heterogeneity was assessed using  $I^2$ , which was defined as low (25%), moderate (50%), or high (75%) according to Higgins and Thompson.<sup>12</sup>

**Table 2. Study Data**

Study	No. of Participants	Mean Age, y (SD)	Men/Women, n (%)	Patients With TAA (n)	Synchronous; Metachronous TAA (n)	Location of the Aneurysm—Asc; Desc; Arch (n)	TAA—Men/Women, n (%)
Larsson et al, 2011 <sup>15</sup>	354	74 (NR)	274 (77.4)/80 (22.6)	100	100; NR	12; 94; 6	62 (62)/38 (38)
Chaer et al, 2012 <sup>4</sup>	1082	74.6 (9)	724 (66.9)/358 (33.1)	253	117; 136	NR	143 (68.5)/105 (41.5)
Takigawa et al, 2012 <sup>18</sup>	157	72.7 (7.5)	128 (82)/29 (18)	13	13; NR	2; 8; 3	NR
Agricola et al, 2013 <sup>14</sup>	1305	NR	1034 (79.2)/271 (20.8)	137	137; NR	52; NR; 85	66 (48)/71 (52)
Wallinder et al, 2018 <sup>17</sup>	217	75 (NR)	0 (0)/217 (100)	67	NR; NR	8; 53; 2	NR/67 (100)
Dombrowski et al, 2019 <sup>16</sup>	218	74 (NR)	136 (62.4)/82 (37.6)	40	40; NR	19; 13; 8	20 (50)/20 (50)

AAA indicates abdominal aortic aneurysms; Arch, aortic arch; Asc, ascending thoracic aorta; CT, computed tomography; Desc, descending thoracic aorta; NR, not reported; and TAA, thoracic aortic aneurysm.



**Figure 2.** Forest plot analyzing the prevalence of synchronous/metachronous thoracic aortic aneurysm in patients with known abdominal aortic aneurysm.

AAA indicates abdominal aortic aneurysm; and SM-TAA, synchronous/metachronous thoracic aortic aneurysm.

Sensitivity analysis was performed according to the diagnostic method used (computed tomography [CT] scan or magnetic resonance/magnetic resonance-angiogram versus transthoracic echocardiography), to the definition for AAA used (only patients admitted for AAA repair versus all patients with an abdominal aortic diameter  $\geq 3$  cm) and type of patients included (both men and women versus only women).

**Risk of Bias**

We adapted and used the Critical Appraisal Skills Program cohort study checklist to assess for risk of bias, in which we categorized 9 items as having high, unclear, or low risk of bias.<sup>13</sup> Two authors (R.G.M. and A.L.) independently assessed each included paper. The overall risk of bias for each study was divided as high- or low-risk, with high-risk studies considered those in which at least 2 items were assessed at a high risk of bias, or where  $>3$  items were rated as unclear.

**RESULTS**

**Included Studies**

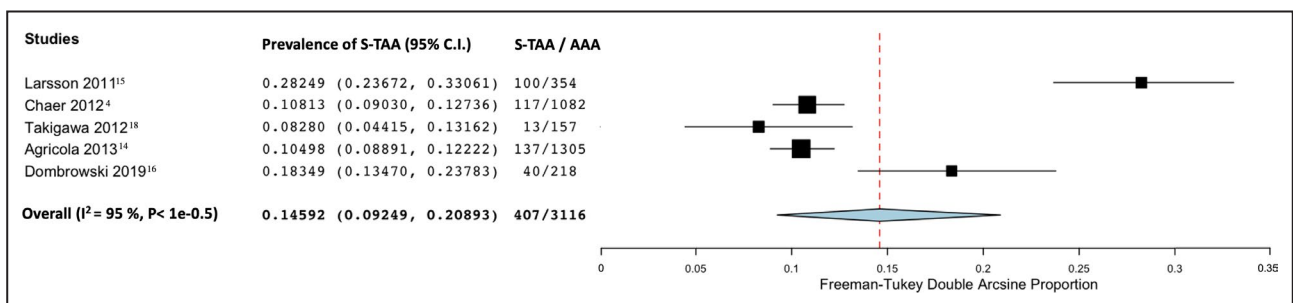
The search yielded 3563 papers which resulted in 3197 articles after duplicates were removed. After title and

abstract screening, 44 papers were included in the full-text assessment. Of these, 6 articles were included in the review.<sup>4,14-18</sup> The reasons for exclusion of the remainder 38 full-text articles assessed are detailed in Figure 1.

**Study Characteristics and Demographic Data**

Overall, 3333 patients with known AAA were included. Of these, 610 were found to have an SM-TAA.

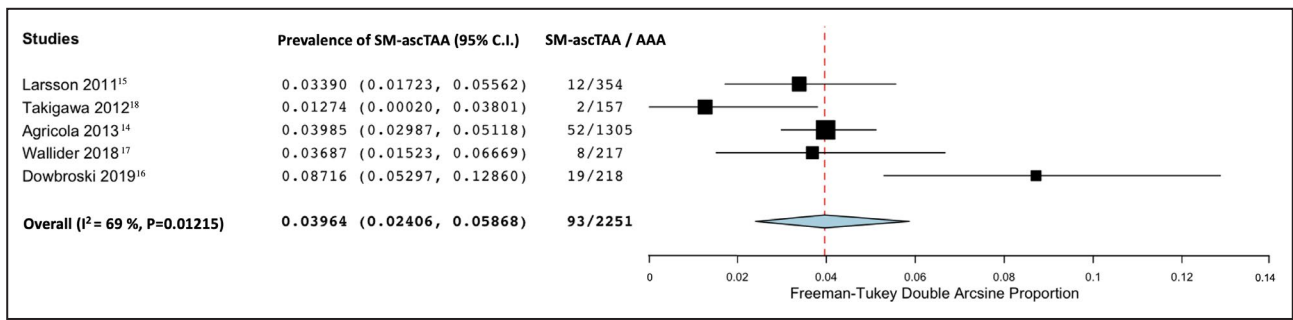
Definitions of both AAA and TAA varied across studies (Table 1). Four papers<sup>4,15-17</sup> defined AAA as an increase in the aortic diameter  $\geq 30$  mm and 2 papers<sup>14,18</sup> did not give precise definition of AAA. However, both of these later studies included patients who were undergoing elective AAA repair, so we can assume the definition to be a diameter of, at least 50 mm.<sup>14,18,19</sup> The diagnostic method of TAA also varied: CT in 4 studies<sup>15-18</sup>; CT, magnetic resonance, or magnetic resonance-angiogram in one,<sup>4</sup> and transthoracic echocardiography in another.<sup>14</sup> Specific demographic data, including risk factors, for all participants in both groups (synchronous/metachronous and only AAA patients) were only detailed in 2 studies.<sup>4,16</sup> Mean age in the total cohort varied between 72.5 and 75 years. Most patients in the cohort were men, except for the paper by Wallinder et al<sup>17</sup> which only analyzed female patients (Table 2).



**Figure 3.** Forest plot analyzing the prevalence of synchronous thoracic aortic aneurysm in patients with known abdominal aortic aneurysm.

AAA indicates abdominal aortic aneurysm; and S-TAA, synchronous thoracic aortic aneurysm.





**Figure 4.** Forest plot analyzing the prevalence of synchronous/metachronous ascending thoracic aortic aneurysm in patients with known abdominal aortic aneurysm.

AAA indicates abdominal aortic aneurysm; and SM-ascTAA: synchronous/metachronous ascending thoracic aortic aneurysm.

Only 1 paper<sup>4</sup> provided with individualized data for both synchronous and metachronous TAAs, 4 papers<sup>14–16,18</sup> only reported on synchronous TAAs and another included both synchronous and metachronous TAAs but did not report the specific number of each.<sup>17</sup>

Three papers provided the indications for chest imaging: in the Agricola et al<sup>14</sup> study the reason was to measure the ascending aorta and aortic arch diameter and in the other 2 studies the majority of patients performed a chest CT for non-aortic related problems, mostly for pulmonary indications (74% in Chaer et al<sup>4</sup> and 68% in Dombrowski et al<sup>16</sup>). Information on specific aortic diameter of the TAAs was only available in 2 studies.<sup>4,17</sup> In the Wallider et al<sup>17</sup> study, one ascending aortic aneurysm had ≥60 mm and 14 descending aortic aneurysms had ≥55 mm leading to 13 of the patients having undergone repair. In the Chaer et al<sup>4</sup> study they reported that 61 of 253 patients underwent repair, ruptured, or had a TAA >55 mm, and 13 patients died from a ruptured TAA. Mortality from TAA was not described in any other paper.

**Risk of Bias**

Overall, the risk of bias was considered to be high. The main source of risk of bias was the absence of adjusting for key risk factors, which occurred in all studies,

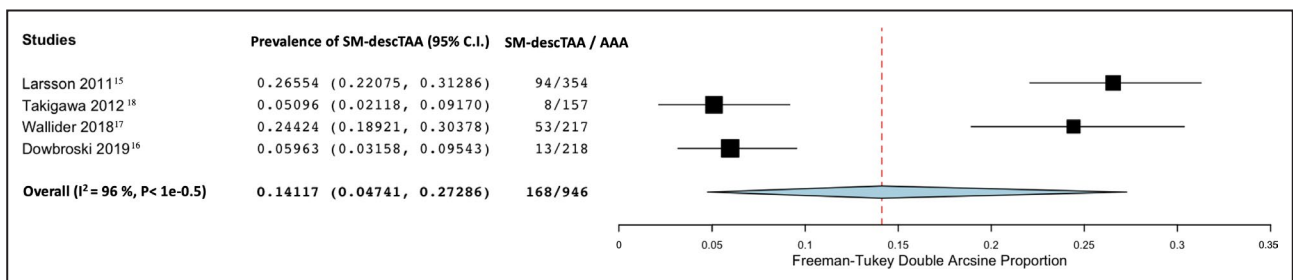
such as age, smoking, and hypertension. Additional sources of risk of bias were: the selective recruitment of patients undergoing AAA repair in the studies by Agricola et al<sup>14</sup> and Takigawa et al,<sup>18</sup> rather than including every patient with AAA (ie, diameter ≥30 mm); and in the way the outcome (prevalence of TAA) was measured in the study by Agricola et al,<sup>14</sup> which used transthoracic echocardiography only (Figure S1).

**Prevalence of Synchronous/ Metachronous TAA in Patients With Known AAA**

Overall, we found that 19.2% of patients with AAA had an SM-TAA (95% CI, 12.3–27.3; I<sup>2</sup>=96%; 6 studies; 3333 participants)—Figure 2.

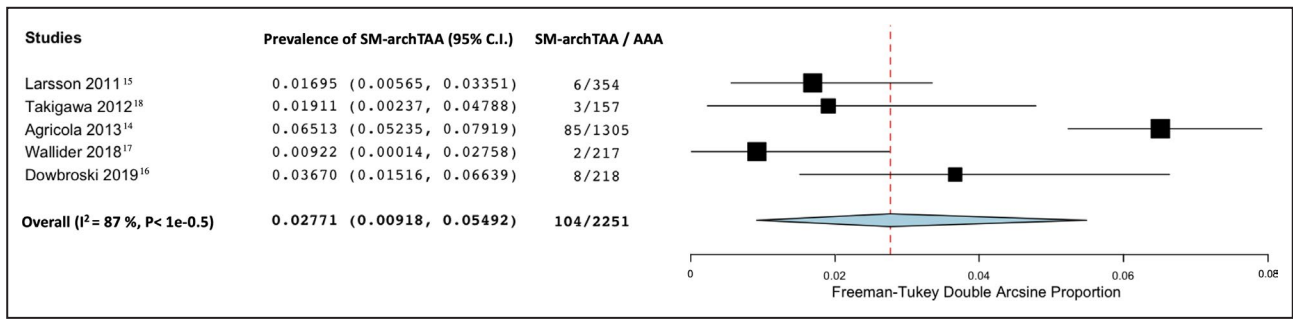
**Individualized Prevalence of Synchronous and Metachronous TAA in Patients With Known AAA**

The prevalence of synchronous TAA in patients with known AAA was 14.6% (95% CI, 0.09–20.9; I<sup>2</sup>=94%; 5 studies; 3116 participants)—Figure 3. Only the study from Chaer et al<sup>4</sup> specified the number of metachronous TAAs in patients with known AAA and found a prevalence of 12.7%.



**Figure 5.** Forest plot analyzing the prevalence of synchronous/metachronous descending thoracic aortic aneurysm in patients with known abdominal aortic aneurysm.

AAA indicates abdominal aortic aneurysm; and SM-descTAA, synchronous/metachronous descending thoracic aortic aneurysm.



**Figure 6.** Forest plot analyzing the prevalence of synchronous/metachronous thoracic aortic arch aneurysm in patients with known abdominal aortic aneurysm.

AAA indicates abdominal aortic aneurysm; and SM-archTAA: synchronous/metachronous arch thoracic aortic aneurysm.

### Prevalence of Synchronous/ Metachronous TAA in Patients With Known AAA According to Anatomic Location

The prevalence of SM-TAA in patients with known AAA according to the anatomic location of the TAA was 4% in the ascending thoracic aorta (95% CI, 2.4–5.7; I<sup>2</sup>=69%; 5 studies; 2251 participants)—Figure 4; 14.1% in the descending thoracic aorta (95% CI, 4.7–27.3; I<sup>2</sup>=96%; 4 studies; 946 participants)—Figure 5 and 2.8% involving the aortic arch (95% CI, 0.9–5.5; I<sup>2</sup>=87%; 5 studies; 2251 participants)—Figure 6.

### Prevalence and Risk of Synchronous/ Metachronous TAA in Patients With Known AAA According to Sex

We found that 15.2% of male patients with AAA had an SM-TAA (95% CI, 7.1–25.6; I<sup>2</sup>=97%; 4 studies; 2168 participants)—Figure 7. In female patients, the prevalence was higher: 30.7% of female patients with AAA had an SM-TAA (95% CI; 25.2–36.5; I<sup>2</sup>=71%; 5 studies; 1008 participants)—Figure 8.

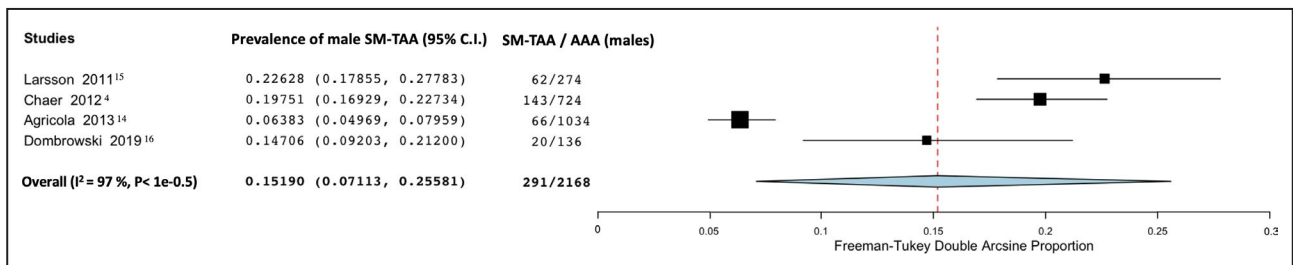
Comparing both groups, women with AAA had a 2-fold increased risk of having SM-TAA compared with men with AAA (RRs, 2.16; 95% CI, 1.32–3.55; I<sup>2</sup>=90%; 4 studies; 2168 participants)—Figure 9.

### Risk of Synchronous/Metachronous TAA in Patients With Known AAA According to Other Risk Factors

Information on risk factors in both groups (SM-TAA and only AAA patients) was only available in 2 studies.<sup>4,16</sup> Overall, diabetes mellitus was associated with a 43% decreased risk of having SM-TAA and AAA (RRs, 0.57; 95% CI, 0.41–0.80; I<sup>2</sup>=0%; 2 studies; 1007 participants)—Figure 10. All other identified risk factors: smoking; hypertension; chronic obstructive pulmonary disease; family history of aortic aneurysm; and hyperlipidemia were not associated with an increased or decreased risk of having an SM-TAA and AAA (Table 3).

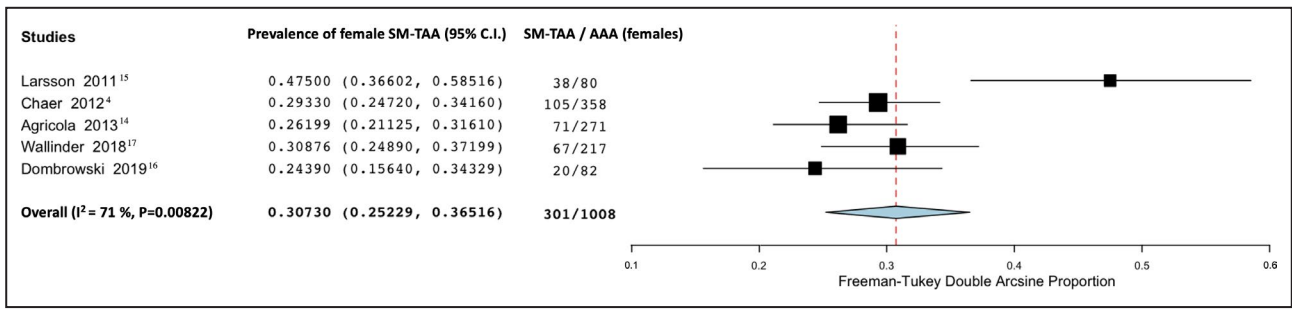
### Sensitivity Analysis

To analyze the impact of using different diagnostic methods (namely transthoracic echocardiography), different definitions for AAA and only including female patients in the study, we performed a sensitivity analysis evaluating these effects (Table 4). Excluding the paper from Agricola et al,<sup>14</sup> which used transthoracic echocardiography as the diagnostic method to screen for TAAs and screened only for ascending and arch aneurysms, showed an increase in the prevalence (19.2% versus 21.5%). However, when analyzing according to the anatomic location the prevalence remained the same on ascending TAAs and was lower on arch TAAs (2.8%



**Figure 7.** Forest plot analyzing the prevalence in men of synchronous/metachronous thoracic aortic aneurysm in patients with known abdominal aortic aneurysm.

AAA indicates abdominal aortic aneurysm; and SM-TAA, synchronous/metachronous thoracic aortic aneurysm.



**Figure 8.** Forest plot analyzing the prevalence in women of synchronous/metachronous thoracic aortic aneurysm in patients with known abdominal aortic aneurysm. AAA indicates abdominal aortic aneurysm; and SM-TAA, synchronous/metachronous thoracic aortic aneurysm.

versus 1.9%). Also, when we only included papers using a definition of  $\geq 30$  mm<sup>4,15–17</sup> for AAAs the prevalence of SM-TAA also increased (19.2% versus 25%).

## DISCUSSION

The main findings of this review were: (1) the overall prevalence of SM-TAA in patients with a known AAA was 19.2% (95% CI, 12.3–27.3) and (2) the prevalence of SM-TAA was higher in women—30.7% (95% CI, 25.2–36.5) versus 15.2% (95% CI, 7.1–25.6)—with a 2-fold increase in risk.

These findings are surprising as almost a fifth of every patient with an AAA will have a TAA and that number increases to almost a third in women.

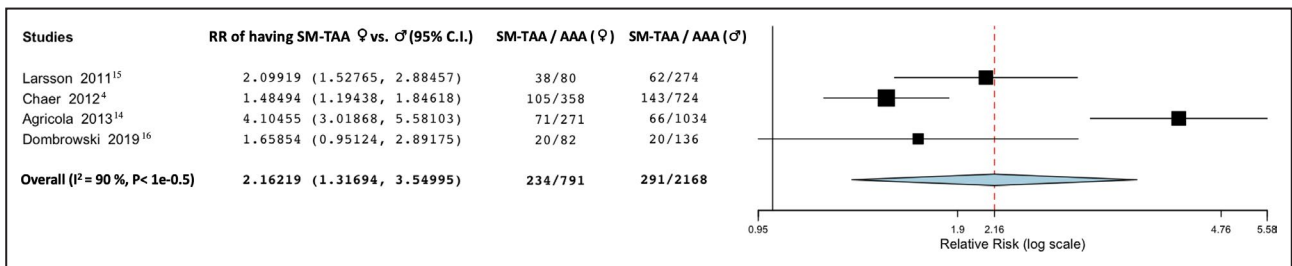
Screening strategies for AAA with an abdominal ultrasound have shown to be effective, reducing the incidence in aneurysm rupture rate and improvement of care in a cost-effective fashion.<sup>3</sup> Contrary to AAAs, implementing a screening strategy for TAAs is difficult, since for an accurate diagnosis, a chest CT is usually necessary. Transthoracic echocardiography might find some but certainly not all TAAs, especially in the descending thoracic aorta. We found this in our sensitivity analysis: the prevalence increased (19.2% versus 21.5%) when we excluded the study from Agricola et al.<sup>14</sup> In fact, in this latter study,<sup>14</sup> which used only transthoracic echocardiography to screen for TAAs,

the prevalence described for synchronous TAAs in patients with known AAA was only 10.5%, which is probably because of the fact that descending TAAs were not screened (Table 4).

The absence of a timely diagnosis has led to a lot of TAAs passing undiagnosed until a complication occurs, such as rupture, which is usually fatal.<sup>20,21</sup> A TAA diagnosed before rupture is a potential life saved and this is usually made accidentally. We found that 19.2% of AAAs have an SM-TAA, this means that screening every patient with a known AAA with a chest CT might be useful. Moreover, death attributable to rupture of other aneurysms, such as TAAs, is already a problem recognized in long-term follow-up of AAA repair.<sup>4,6,7,22,23</sup>

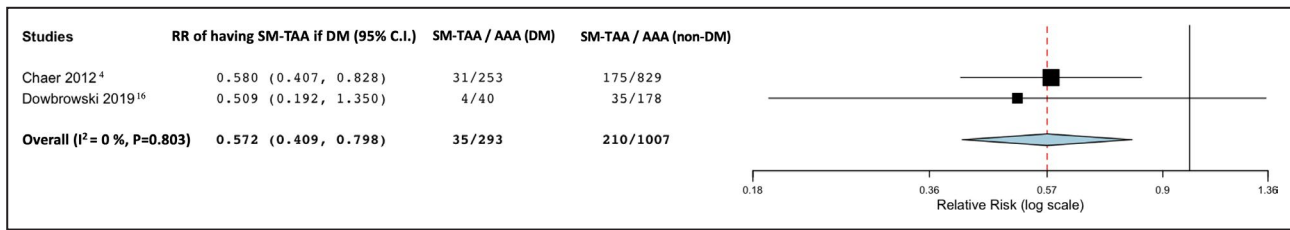
Currently, there are no clear indications in the current Society of Vascular Surgery guidelines<sup>19</sup> about full aortic imaging when an AAA is diagnosed. Although more research is needed to demonstrate cost-effectiveness and the real impact of these SM-TAA, we believe TAA screening in patients with a known AAA should probably become common practice since 19.2% is not negligible.

The difference found between male and female sex is striking. It has been known that women have a lower threshold for aneurysm rupture and have worse outcomes after AAA repair, even when operated at smaller diameters.<sup>24,25</sup> No one has yet clearly understood why this occurs. The higher prevalence of synchronous/metachronous thoracic and abdominal aortic



**Figure 9.** Forest plot analyzing relative risk of female sex comparing with male sex on the prevalence of synchronous thoracic aortic aneurysm in patients with known abdominal aortic aneurysm. AAA indicates abdominal aortic aneurysm; and SM-TAA, synchronous/metachronous thoracic aortic aneurysm.





**Figure 10.** Forest plot analyzing relative risk of diabetes mellitus on the prevalence of synchronous thoracic aortic aneurysm in patients with known abdominal aortic aneurysm. AAA indicates abdominal aortic aneurysm; DM, diabetes mellitus; RR, relative risk; and SM-TAA, synchronous/metachronous thoracic aortic aneurysm.

aneurysms in women, might indicate that aneurysm disease has a different pathophysiology in the female sex, with a different and probably more aggressive and systemic behavior than in men. This might be one of the causes for these worse long-term outcomes found in women. Understanding this fact might lead us to increase our diagnostic suspicion for synchronous and metachronous TAAs and lead us to better surveillance and ultimately improved care.

Because of lack of data, we were not able to analyze in-depth other risk factors which might be predictive of higher prevalence of SM-TAA. We found diabetes mellitus to be negatively associated with the risk of having SM-TAA and AAA, however, this data were only available in 2 studies,<sup>4,16</sup> which limits our findings. In the paper from Chaer et al<sup>4</sup> positive predictors of SM-TAA were Black race; family history of TAA; hypertension; and obesity; and negative predictors were diabetes mellitus, infra-renal location of the AAA; and smoking.

This review has some limitations, the difference in study designs on diagnostic method and definitions of both AAA and TAAs brings some clinical and possibly statistical heterogeneity to our results in general. The fact that the data retrieved was not age-standardized

also limits our findings, and explains, at least, partially, the statistical heterogeneity. The lack of data about risk factors in both groups (synchronous and AAA-only patients), such as smoking or hypertension, limited our analysis on possible confounding or predictive factors for the presence of SM-TAA. Other important data that were not available across all studies was the size of the TAAs found, the number of TAAs that ruptured, and their mortality before repair, which limits our analysis about risk and the prognosis of these aneurysms.

Further studies are needed to understand the clinical behavior of synchronous and metachronous TAAs in AAA patients (including their morbidity and mortality), what is the true impact of screening patients with an AAA with a chest CT, to assess the cost-effectiveness of such a screening program and to understand their relationship with the female sex.

A feasible observational study would be to compare 2 time periods: pre- and post-SM-TAA screening with a chest CT in all patients with a known AAA to address the impact of screening in the number of treatable/near treatable TAAs and the number of preventable ruptured TAAs and deaths. Also, using large registry data would be useful to identify other clinical characteristics that might be more common in patients with synchronous or metachronous aortic aneurysms.

**Table 3.** Relative Risk of Having a Synchronous TAA and AAA Compared With Patients With AAA Only Across the Different Risk Factors

Risk Factor	Relative Risk
Diabetes mellitus	0.57 (95% CI, 0.41–0.80; I <sup>2</sup> =0%; 2 studies; 1007 participants)
Smoking	0.97 (95% CI, 0.85–1.10; I <sup>2</sup> =62%; 2 studies; 1007 participants)
Hypertension	1.01 (95% CI, 0.94–1.01; I <sup>2</sup> =70%; 2 studies; 1007 participants)
Hyperlipidemia	1.10 (95% CI, 0.89–1.3; I <sup>2</sup> =58%; 2 studies; 1007 participants)
COPD	1.09 (95% CI, 0.93–1.28; I <sup>2</sup> =0%; 2 studies; 1007 participants)
Family history of AAA/TAA	2.37 (95% CI, 0.97–5.77; I <sup>2</sup> =35%; 2 studies; 1007 participants)

AAA indicates abdominal aortic aneurysm; COPD, chronic obstructive pulmonary disease; and TAAs, thoracic aortic aneurysms.

## CONCLUSIONS

This meta-analysis increases the evidence about the presence of synchronous/metachronous TAA in patients with known AAA. The higher prevalence of these aneurysms in women is striking and might explain one of the aspects why worse outcomes on follow-up of AAA are observed in women and shows the importance of aortic screening in women.

To improve short- and long-term outcomes after AAA repair, the authors recommend that routine screening of synchronous and metachronous TAAs and their clinical impact should be more thoroughly studied, since 19.2% of AAAs with an SM-TAA is not a negligible number.

**Table 4. Sensitivity Analysis**

Synchronous/Metachronous TAA in Patients With Known AAA	Prevalence (%)
<b>Overall Prevalence of SM-TAA in Patients With Known AAA</b>	<b>19.2 (95% CI, 12.3–27.3; I<sup>2</sup>=96%; 6 studies; 3333 participants)</b>
Studies using CT and/or MR for the diagnosis of TAA	21.5 (95% CI, 15.4–28.2; I <sup>2</sup> =90%; 5 studies; 2028 participants)
Studies using TE for the diagnosis of TAA	10.5 (95% CI, 8.9–12.2, 1 study; 1305 participants)
Using AAA definition of a diameter ≥30 mm	25.0 (95% CI, 20.6–29.7; I <sup>2</sup> =76%; 4 studies; 1871 participants)
Including only AAA patients admitted for surgery	10.2 (95% CI, 8.6–11.8; I <sup>2</sup> =0%; 2 studies; 1462 participants)
Including both male and female patients	17.2 (95% CI, 10.2–25.5; I <sup>2</sup> =96%, 4 studies, 3116 participants)
Studies only analyzing female patients	30.9 (95% CI, 24.9–37.2)
<b>Overall Prevalence of Synchronous/Metachronous Ascending TAAs in Patients With Known AAA</b>	<b>4% (95% CI, 2.4–5.7; I<sup>2</sup>=69%; 5 studies; 2251 participants)</b>
Studies using CT and/or MR for the diagnosis of ascending TAA	4% (95% CI, 1.7–7.0; I <sup>2</sup> =76%; 4 studies; 946 participants)
<b>Overall Prevalence of Synchronous/Metachronous Arch TAAs in Patients With Known AAA</b>	<b>2.8% (95% CI, 0.9–5.5; I<sup>2</sup>=87%; 5 studies; 2251 participants)</b>
Studies using CT and/or MR for the diagnosis of arch TAA	1.9% (95% CI, 1.0–3.1; I <sup>2</sup> =23%; 4 studies; 946 participants)

AAA indicates abdominal aortic aneurysm; CT, computed tomography; MR, magnetic resonance; SM-TAA, synchronous/metachronous thoracic aortic aneurysms; TAAs, thoracic aortic aneurysms; and TE, transthoracic echocardiography.

## ARTICLE INFORMATION

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Gouveia e Melo and Silva Duarte conceived the idea for the protocol and made the main contribution to planning and preparation of timelines for completion. Gouveia e Melo and Lopes analyzed all papers, extracted the data, and analyzed the risk of bias. Gouveia e Melo performed the statistical analysis. Caldeira and Alves analyzed the data and confirmed the statistical analysis. Gouveia e Melo designed the tables and wrote the first draft of the manuscript, which was then reviewed and amended by Alves, Caldeira, Fernandes e Fernandes, and Pedro. All authors then approved the final written manuscript. Gouveia e Melo is the guarantor for the work.

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### Disclosures

None.

### Supplementary Material

Table S1  
Figure S1

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# **SUPPLEMENTAL MATERIAL**

**Table S1. Research strategy.**

1. Exp Aortic Aneurysm, Thoracic/
2. Exp Aneurysm, Ruptured/
3. ((thoracoabdominal or thoraco-abdominal or thorax or thoracic) adj3 (aneurysm or dilated or ectasia) adj3 (aorta or aortic)).ti,ab,kw.
4. 1 or 2 or 3
5. Incidence/ or incidence.ti.ab.kw.
6. Epidemiologic studies/
7. Cohort studies/ or cohort.ti.ab.kw.
8. Prevalence/ or prevalence.ti.ab.kw
9. 5 or 6 or 7 or 8
10. 4 and 9
11. Exp animals/ not humans.sh.
12. 10 not 11



**Figure S1. Risk of Bias – CASP cohort study checklist.**

	1. Are the results of the study valid?	2. Was the cohort recruited in an acceptable way?	3. Was the exposure accurately measured to minimise bias?	4. Was the outcome accurately measured to minimise bias?	5. a) Have the authors identified all important confounding factors – age, smoking, hypertension	5. b) Have they taken account of the confounding factors in the design and/or analysis?	9. Do you believe in the results?	10. Can the results be applied to the local population?	11. Do the results of this study fit with other available evidence?	Overall risk of bias: high or low
Larsson 2011 <sup>15</sup>	L	L	L	L	H	H	L	L	L	H
Chaer 2012 <sup>4</sup>	L	L	L	L	L	H	L	L	L	L
Takigawa 2012 <sup>18</sup>	L	H	U	L	H	H	L	L	L	H
Agricola 2013 <sup>14</sup>	L	H	U	H	H	H	L	L	L	H
Wallinder 2018 <sup>17</sup>	L	L	L	L	H	H	L	L	L	H
Dombrowski 2019 <sup>16</sup>	L	L	L	L	L	H	L	L	L	L

Original CASP items	Adapted CASP items	Reasons for downgrading
1. Did the study address a clearly focused issue?	1. Did the study address a clearly focused issue?	
2. Was the cohort recruited in an acceptable way?	2. Was the cohort recruited in an acceptable way?	Not including every AAA with a diameter equal or higher than 30mm
3. Was the exposure accurately measured to minimise bias?	3. Was the exposure accurately measured to minimise bias?	No clear explanation of how the diagnosis of AAA was obtained
4. Was the outcome accurately measured to minimise bias?	4. Was the outcome accurately measured to minimise bias?	Did not use either chest MR or CT to diagnose a TAA
5. (a) Have the authors identified all important confounding factors?	5. (a) Have the authors identified all important confounding factors – age, smoking, hypertension	These risk factors have not been identified and quantified in the overall cohort and outcome group
5. (b) Have they taken account of the confounding factors in the design and/or analysis?	5. (b) Have they taken account of the confounding factors in the design and/or analysis?	No adjustment has been made for confounding factors (age, smoking, hypertension)
6. (a) Was the follow up of subjects complete enough?	Not used – not applicable	
6. (b) Was the follow up of subjects long enough?	Not used – not applicable	
7. What are the results of this study?	Not used – not applicable (open question format)	
8. How precise are the results?	Not used – not applicable (open question format)	
9. Do you believe the results?	9. Do you believe the results?	No clear definition of TAA and methods used for diagnosis are provided
10. Can the results be applied to the local population?	10. Can the results be applied to the local population?	The population is not a valid cohort for AAA patients in a hospital/community setting
11. Do the results of this study fit with other available evidence?	11. Do the results of this study fit with other available evidence?	The results are not in concordance with the overall available data regarding synchronous TAA and AAA
12. What are the implications of this study for practice?	Not used – not applicable (open question format)	

Risk of Bias using CASP cohort study checklist<sup>13</sup>. H: High risk of bias; U: Unclear risk of bias; L: Low risk of bias. This tool was adapted from the CASP cohort study checklist, in which we used 9 out of the 14 original items. The table below shows the changes made and what was considered to downgrade the risk of Bias.