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1 **Title page**

2 **A systematic review summarizing local vascular characteristics of the aneurysm wall to**
3 **predict progression and rupture risk of abdominal aortic aneurysms**

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18

19 **Article highlights**

20 **Type of research:** Systematic review

21 **Key finding:** Measures of local vascular characteristics of the aortic wall might predict
22 abdominal aortic aneurysm progression. Measures of metabolism and calcification, but not
23 intraluminal thrombus and compliance, have potential predictive value for aneurysm growth.

1 Only local aorta aneurysm metabolism could potentially be related to abdominal aortic aneurysm
2 rupture.

3 **Take home message:** Current measures of local vascular characteristics of the aortic wall may
4 predict abdominal aortic aneurysm growth and/or rupture, especially measures of aortic wall
5 metabolism and calcification.

6 **Table of contents summary**

7 This systematic review demonstrated that current measures of local vascular characteristics of
8 the aortic wall may predict abdominal aortic aneurysm growth, mainly by assessing aortic wall
9 metabolism and calcification. Aneurysm rupture might have a relation with metabolism. These
10 measures could improve prediction of aneurysm growth and rupture.

11

12 **Abstract**

13 **Objective.** Rupture risk prediction of abdominal aortic aneurysms (AAA), and hence clinical
14 decision making on the need for surgery, is currently based on AAA diameter and growth rate.
15 Unfortunately, these measures provide limited predictive information. This study summarized
16 measures of local vascular characteristics of the aneurysm wall that, independent of AAA size,
17 could predict AAA progression and AAA rupture.

18 **Method.** Pubmed and Web of Science were systematically searched up to September 13th, 2021
19 to identify relevant articles investigating the relationship between local vascular characteristics
20 of the aneurysm wall and AAA growth or rupture in humans. Quality assessment was performed
21 with the ROBINS-I tool. All included articles were divided in four types of measure of arterial
22 wall characteristics; metabolism, calcification, intraluminal thrombus and compliance.

1 **Results.** Twenty articles were included. Metabolism of the aneurysm wall, especially measured
2 with ultra-small superparamagnetic iron oxide uptake, and calcification were significantly related
3 to AAA growth. Higher intraluminal thrombus volume and thickness was in one study positively
4 correlated to AAA growth and in another study negatively correlated. AAA compliance
5 demonstrated no correlation with AAA growth and rupture. Aneurysmal wall characteristics
6 showed no association with AAA rupture. However, metabolism measured by ultra-small
7 superparamagnetic iron oxide uptake, but none of the other measures, showed a trend toward a
8 relation to AAA rupture, although not statistically significant.

9 **Conclusion.** Current measures of aortic wall characteristics have potential to predict AAA
10 growth, especially measuring metabolism and calcification. Evidence regarding AAA rupture is
11 scarce and although more work is needed, aortic wall metabolism could potentially be related to
12 AAA rupture. This highlights the role of aortic wall characteristics in the progression of AAA,
13 but also the potential to improve prediction of AAA growth and rupture.

14 **Key words.** Abdominal aortic aneurysm, growth, rupture, aortic wall
15

16 **Introduction**

17 Abdominal aortic aneurysm (AAA) has a multifactorial pathogenesis, which is characterized by
18 elastin and collagen degradation in the aortic wall, apoptosis of vascular smooth muscle cells and
19 the infiltration of leukocytes into the aneurysmal tissue^{1,2}. Furthermore, vascular inflammation is
20 the key process underlying AAA development and progression³⁻⁶. AAA rupture is a devastating
21 complication that occurs when the local wall stress exceeds the wall strength and results in an
22 intra-abdominal hemorrhage with mortality of up to 85%⁷. Generally, AAA patients are
23 asymptomatic, and therefore mostly diagnosed as an incidental observation on imaging

1 performed for other pathology, or when they present with rupture⁸. This highlights the
2 importance for accurate prediction of the risk for AAA rupture.

3 Current predictions of the AAA rupture risk, and consequently the indications for preventive
4 treatment, are based on the maximum anterior-posterior diameter, measured perpendicular to the
5 center line with three-dimensional reconstructed computed tomography images, and growth rate.
6 Studies showed that the risk of AAA rupture is strongly associated with AAA diameter⁹⁻¹¹.

7 However, a recent study of Oliver-Williams et al.¹² included 18,652 men with small (3 – 4.4 cm)
8 and medium (4.5 – 5.4 cm) AAAs. Thirty-one men had ruptured AAA during surveillance,
9 resulting at a risk of 0.03% per annum for men with small AAAs and 0.28% for medium
10 AAAs¹². In a cohort of 192 ruptured AAAs, 7.2% of these ruptured AAAs had a diameter
11 smaller than 5.5 cm¹³. Rupture rates of untreated large AAAs turn out to be lower (ranging
12 between 3.5% to 6.3%) than currently reported in literature¹⁴. Laine *et al.*¹⁵ also demonstrated
13 that 6% of men and 12% of women had a ruptured AAA under threshold for repair¹⁵. This
14 emphasizes the need for additional, personalized measures that can predict the risk of AAA
15 rupture, independently of AAA size, in order to optimize personalized patient care.

16 The pathogenesis of AAA involves several crucial mechanisms taking place in the aortic wall,
17 including inflammation^{4,5}, biomechanical changes³, and calcification^{4,6}. Accordingly, these
18 processes affect the functional aortic wall characteristics that, subsequently, contribute to the
19 increased risk for AAA growth and rupture. Possibly, directly measuring these aortic wall
20 characteristics, including functional changes and inflammation, might better aid in the prediction
21 of AAA progression and rupture risk than AAA size. Therefore, the aim of this systematic
22 review is to summarize potential measures of aneurysmal wall characteristics that, independent

1 of AAA size, predict AAA progression and AAA rupture in AAA patients who are currently not
2 yet suitable for treatment.

3

4 **Method**

5 This review was conducted and reported in accordance with the 2009 PRISMA statement. An
6 identifier (CRD42020177659) of this protocol was assigned at PROSPERO
7 (<https://www.crd.york.ac.uk/prospero/>). The databases PubMed and Web of Science were
8 searched May 11th, 2020 and updated on September 13th, 2021. Only primary sources were
9 included in the review. References of included studies and secondary sources were manually
10 searched for additional relevant articles that were missed by electronic search. The search
11 strategy for each database is shown in Supplemental Table I. The search strategy included the
12 different elements of the Population, Intervention, Comparison and Outcome (PICO) tool. The
13 target population consisted of adult patients with AAA, who have not yet been treated.
14 “Interventions” included measures of local vascular wall characteristics in the aneurysm wall.
15 These distinct “interventions” were compared among each other. The outcome was defined as
16 AAA growth and/or rupture.
17 Eligible studies should investigate at least one measure of aneurysmal wall characteristics in
18 combination with its prognostic value for AAA rupture risk and/or AAA growth, preferably
19 independent of current clinically used risk factor, e.g., baseline aorta diameter. Local aneurysmal
20 wall characteristics was defined as vascular functional properties of the aortic wall. Exclusion
21 criteria consisted of language, other than English, animal studies, and in vitro studies.
22 Identified articles through electronic search were independently screened on titles and abstracts
23 by two authors (JV, MM) using Rayyan¹⁶. Hereafter, potentially relevant studies were

1 independently assessed for eligibility (MM, FdV). Disagreements between the authors were
2 resolved in a consensus meeting (JV, MM, FdV). For quality assessment, the Risk Of Bias in
3 Non-randomized Studies – of Interventions (ROBINS-I) tool¹⁷ was performed on all included
4 studies by two authors (MM, FdV) independently. Differences in quality assessment were solved
5 in a consensus meeting (JV, MM, FdV).

6 All included articles were divided into four groups, based on the vascular wall characteristic that
7 was studied; metabolism, calcification, intraluminal thrombus (ILT) and compliance. When
8 articles studied more than one wall characteristic, the article was classified according to their
9 primary focus. Metabolism was measured using three different measures; 1) 18F
10 fluorodeoxyglucose (FDG) uptake in the aneurysm wall evaluated using positron emission
11 tomography (PET) scan combined with either a computed tomography (CT)¹⁸ or magnetic
12 resonance imaging (MRI) scan¹⁹, which is the most commonly used contrast agent to visualize
13 (aortic) metabolism, 2) 18F sodium fluoride (NaF) uptake evaluated by a PET/CT²⁰ scan and 3)
14 ultra-small superparamagnetic iron oxide (USPIO) uptake evaluated with MRI scan^{21, 22}. All
15 measures used contrast agents to visualize aneurysmal wall inflammation. Calcification was
16 measured with different scores to define the amount of calcification in the aneurysm wall based
17 on ultrasound or CT images in the identified studies²³⁻²⁷. Various parameters related to ILT were
18 reported, including ILT thickness, deposition, area, volume and, volume change, to define ILT,
19 in relation to growth or rupture. CT was used in four studies²⁸⁻³¹ and one study used MRI³² to
20 visualize ILT. All studies used ultrasound (echo-tracking³³) as imaging modality to measure
21 aneurysmal wall compliance described as stiffness and elastic modulus calculated with the same
22 formulas throughout all articles³⁴⁻³⁸.

23

1 **Results**

2 The search strategy identified 806 unique articles that were screened for title and abstract (Figure
3 1). 780 articles were excluded, leaving 26 potentially relevant articles for full-text review. Two
4 studies were excluded for not correlating aneurysmal wall changes with growth and/or rupture
5 and four studies were excluded for not using a measuring type linked to the aneurysm wall. In
6 total, twenty articles fitted the inclusion criteria and were included in this systematic review.

7 **Prediction of AAA growth**

8 **Metabolism.** Studies originally used 18F-FDG to measure local artery metabolism, but these
9 reported conflicting results regarding 18F-FDG uptake in relation to AAA growth (Table I). One
10 prospective study¹⁸ with a small sample size (n=34) demonstrated an inverse correlation between
11 metabolism, as measured by 18F-FDG uptake and AAA growth. Another retrospective study¹⁹
12 with 15 participants found a moderate correlation between the number of FDG hotspots and
13 recent AAA growth¹⁹. More recent studies adopted 18F-NaF and USPIO uptake to measure local
14 artery metabolism. 18F-NaF uptake was studied in a prospective cohort (n=72) and found a
15 positive correlation of 18F-NaF uptake in the aneurysm wall and the AAA growth rate²⁰. Studies
16 investigating USPIO uptake demonstrated a higher growth rate in AAAs with USPIO uptake
17 than in those without USPIO uptake^{21, 22}, of which one prospective study was performed in a
18 cohort of 342 participants and a median follow-up time of 33.5 months²².

19 **Calcification.** Three studies²³⁻²⁵ correlated aneurysmal wall calcification volume with AAA
20 growth (Table II). One retrospective study of Hendy *et al.*²⁴ (n=88) showed no significant
21 relation between aneurysmal wall calcification volume and AAA growth rate. In contrast, two
22 larger studies, one prospective (n=122)²³ and one retrospective (n=414)²⁵ study, demonstrated an

1 inverse effect between aneurysmal wall calcification volume and AAA growth rate, with larger
2 calcification volumes being associated with an attenuated growth rate.

3 ***Intraluminal thrombus.*** Studies investigating ILT in relation to AAA growth used multiple
4 parameters to define presence of ILT in the AAA (Table III). Three small retrospective studies,
5 with a sample size between 26 and 34 participants, showed conflicting results regarding ILT
6 volume in relation to AAA growth. Whilst one study²⁸ found a positive correlation between
7 larger ILT volume and larger growth rate, others found a negative correlation³⁰ or no difference²⁹
8 in ILT volume between high and low growth rate AAAs. Another study investigated a wide
9 variety of parameters defining ILT in a prospective cohort of 41 participant³², and found AAA
10 growth to correlate to baseline ILT volume, but not ILT volume growth.

11 ***Compliance.*** Three studies investigated aneurysmal wall compliance, defined as elastic modulus,
12 stiffness or incremental Young's modulus, in relationship to AAA growth (Table IV). One small
13 (n=7) prospective study with a follow-up time of 48 months found a higher relative increased
14 elastic modulus in fast growing, i.e. 6-12 mm, AAAs (75%-700%) compared to medium, i.e. 5-6
15 mm, (25%-125%) or no growth, i.e. < 2 mm, AAAs (-10%-100%). However, two larger studies
16 with respectively 60³⁴ and 326³⁶ participants found no relationship between elastic modulus or
17 stiffness of the aneurysm wall with AAA growth.

18 **Prediction of AAA rupture**

19 ***Metabolism.*** Two prospective studies investigated the relation between AAA metabolism and
20 rupture events (Table I). One study, with the smallest sample size (n=72)²⁰, recorded three events
21 of rupture and found no difference in rupture events between AAAs with different ¹⁸F-NaF
22 uptake. Another larger multicenter study (n=342)²² mainly focused on the composite endpoint of
23 AAA rupture and repair. When looking at the 17 events of rupture, those AAAs with USPIO

1 uptake had more events of rupture (6.8%) than in those without USPIO uptake (3.7%), albeit not
2 statistically significant different.

3 **Calcification.** Calcification was scored differently in the two studies^{26, 27} investigating its
4 relationship to AAA rupture (Table II). Buijs *et al.*²⁷ performed a retrospective study in a cohort
5 of 334 patients of which 73 patients had a ruptured AAA. Ruptured AAAs had significant
6 higher calcium scores compared to age- and gender-matched intact AAAs. Another retrospective
7 case-control study²⁶ with 108 AAA patients found no difference in calcification classification
8 between ruptured (n=52) and non-ruptured AAAs (n=56).

9 **Intraluminal thrombus.** Haller *et al.*³¹ performed a retrospective study including 51 AAA
10 patients and divided them in four groups; small ruptured AAAs (n=9), small non-ruptured AAAs
11 (n=13), large ruptured AAAs (n=14) and large non-ruptured AAAs (n=15). This study found a
12 significant higher ILT thickness and ILT volume in small ruptured AAAs compared to non-
13 ruptured AAAs (Table III). In contrast, another study including 108 patients²⁶ found a lower ILT
14 volume in ruptured AAAs compared to intact AAAs.

15 **Compliance.** Two studies^{37, 38} investigated aneurysmal wall stiffness and distensibility in relation
16 to rupture (Table IV). One retrospective study (n=132)³⁷ found no difference in aneurysmal wall
17 stiffness, determined by an ultrasonic echo-tracking system, in eleven ruptured AAAs compared
18 to electively operated AAAs. Another study (n=210)³⁸ included 28 ruptured AAAs, and found
19 changes in AAA elastic modulus to be independently predictive for time to rupture.

20 **Quality assessment**

21 As shown in Supplemental Table II, most studies scored a moderate-to-low level of overall bias.
22 Three studies scored an overall bias assessment of 'low' during the quality assessment, meaning
23 no bias was found in these three studies. However, this is because the tool prescribed that when

1 one category scored higher than ‘Low’, the overall score should be similar to this score. Most
2 bias occurred in the pre- and at-intervention domains of the ROBINS-I tool, especially in the bias
3 due to confounding section and the bias in selection of participants section, since not all studies
4 corrected for or reported patient characteristics like age, smoking, AAA diameter and medical
5 history. These quality assessments should be kept in mind during interpretation of the results.

6

7 **Discussion**

8 This review provides an overview of current evidence of vascular characteristics of the
9 aneurysmal wall and their relationship with growth and rupture in patients with an AAA,
10 independent of AAA diameter, who are currently not yet suitable for treatment. First, some
11 vascular characteristics of the aneurysm wall may well relate to AAA progression, with
12 especially measures of local abdominal aortic metabolism and calcification being related to AAA
13 growth. Second, evidence regarding relations between vascular characteristics and AAA rupture
14 is not convincing due to conflicting results and small sample sizes. One measure that might
15 predict AAA rupture is aneurysmal wall metabolism, as assessed by USPIO uptake. However,
16 literature only demonstrated a trend toward an association between USPIO uptake and rupture,
17 which was not statistically significant. Nevertheless, this data represent a signal that warrants
18 further investigation. Therefore, a large prospective trial determining USPIO uptake in AAAs
19 and with larger numbers of ruptured AAAs during follow-up should be performed to better
20 understand its predictive value. Within such studies, specific attention is required for potential
21 between-individual or -group differences, which will ultimately facilitate a more personalized
22 approach in selecting measures to predict future risk for AAA rupture and growth.

1 Several measures of local aortic vascular health in relation to AAA growth were examined, and
2 some measures may provide prognostic insight. Especially measures related to local metabolism
3 seem to relate to AAA growth and USPIO uptake potentially to rupture. Literature presented that
4 AAA growth is more common in metabolic active AAAs than metabolic inactive AAAs¹⁹⁻²². The
5 mechanism of uptake varies between different contrast agents³⁴. 18F-FDG and USPIO uptake is
6 regulated by, respectively, macrophages who undergo classic activation (M1 macrophages) and
7 macrophages with alternative activation (M2 macrophages). M1 macrophages are involved in
8 development of atherosclerosis and M2 macrophages are involved in tissue remodeling and
9 angiogenesis³⁹. Since previous studies suggest a potential role of USPIO uptake for prognostic
10 insight in AAA growth, a potential role for M2 macrophages could thus be suggested and
11 thereby their contribution to tissue remodeling and angiogenesis in AAA development. Possibly,
12 the activation of M2 macrophages represents an attempt within the pathophysiology of AAA
13 development to improve aneurysmal wall characteristics in light of a rapidly growing aneurysm.
14 Nevertheless, both 18F-FDG and USPIO uptake are related to inflammation of the aneurysm
15 wall, which is also involved in AAA progression⁴⁰.

16 Another factor that may correlate to AAA growth is aneurysmal wall calcification, as studies
17 reported that presence of calcification in the aneurysm wall seems to have a protective impact on
18 AAA growth^{23, 25}. During AAA growth, the aneurysm wall is subject to multiple pathological
19 processes among which the loss of vascular smooth muscle cells. Vascular smooth muscle cells
20 regulate the vascular tone and vascular diameter, but may also induce calcification when
21 experiencing stress signals⁴. Whilst this suggests that a faster AAA diameter growth may relate
22 to more calcification, previous studies suggest the opposite^{23, 25}. This implies that calcified cells,
23 perhaps due to the limited deformation capacity of the cells, stops or attenuate the other

1 processes involved in AAA growth. Limited deformation capacity of cells will also change
2 arterial compliance. Demer *et al.*⁴¹ described the complex mechanisms behind vascular
3 calcification and its link to several other components including the vascular compliance.
4 Calcification increases arterial stiffness, which decreases arterial compliance. However,
5 compliance demonstrated no relation with AAA growth. When looking more to the process and
6 components of aortic calcification, literature demonstrates that aortic calcification is also linked
7 to inflammation and metabolism⁴¹. Taking all this into account, aortic calcification represents a
8 multifactorial state of the aortic wall, which could explain why calcification seems related to
9 AAA growth and compliance alone does not.

10 Current studies do not present a strong convincing relationship between the several
11 measurements of vascular characteristics in relation to AAA rupture risk, which could imply that
12 rupture is not only depending on aneurysmal wall characteristics. However, rupture also depends
13 on the strength and thereby the health state of the aneurysm wall. One measure which could
14 therefore potentially be valuable in predicting rupture is metabolism. This should, however, be
15 investigated in a study with larger numbers of ruptured AAAs. Nonetheless, this might be
16 difficult to undertake, since rupture is yet unpredictable and current care is to prevent ruptures.

17 Explaining the reason for aneurysmal wall metabolism to have a potential relation with AAA
18 rupture, the mechanism of the studied contrast agents should be further clarified. When
19 considering the contrast agents investigated in the different studies, both 18F-FDG and USPIO
20 demonstrate a different distribution and pattern in uptake⁴⁰. 18F-FDG is found more often in the
21 AAA shoulder and USPIO in the main body. Additionally, USPIO uptake is slower than 18F-
22 FDG⁴². This may indicate that USPIO is only measured when the inflammation process is
23 advanced, since this will result in a sufficient concentration of inflammatory cells to cause strong

1 signal of USPIO uptake, and therefore have a more convincing correlation with AAA growth and
2 potentially rupture than 18F-FDG.

3 Rupture is not inextricably linked to growth but also can occur independently of AAA growth.

4 One measure that demonstrated no conspicuous relationship with AAA growth was ILT volume
5 and thickness. This can be partly explained by the different parameters that were studied and the
6 small sample sizes of the studies. This also applied to its evidence with regard to AAA rupture.

7 However, a review by Schmitz-Rixen *et al.*⁴³ indicated that ILT causes hypoxia in the aneurysm
8 wall, which leads to more inflammation, apoptosis of vascular smooth muscle cells and wall
9 degradation and thereby activate AAA metabolism⁴⁴⁻⁴⁶ that, in turn, could lead to AAA rupture.
10 Therefore, ILT and aortic wall metabolism could potentially give a good description of current
11 state and strength of the aneurysm wall, which also determines whether the aneurysm wall is
12 prone to rupture.

13 A limitation of this review is the relatively low number of participants within each study,
14 inconsistency in end-points (and its associated methodology) and the low event rates in the
15 included articles. Because of these limitation we refrained from performing meta-analysis. These
16 limitations should be taken into consideration when interpreting the results of this review, and
17 when setting up future studies on this topic. Since defined measures, especially focusing on
18 metabolism, could be expensive or complicated, it is important to know whether selection bias of
19 participants narrows the group who benefit from these measures. Fortunate, quality assessment
20 found a low risk of bias, which implies that metabolic measures seem applicable to most AAA
21 patients possible except those with renal dysfunction, who were excluded in two studies.

22 However, more research is needed in larger trials to confirm and define which AAA patients
23 would benefit most from these measurements. Another limitation was the focus only on local

1 characteristics of the aneurysm wall. AAA influences both locally as systemically the patient's
2 health⁴⁷. There are multiple studies who investigated the predictive value of surrogate measures,
3 like biomechanical properties^{48, 49} and biomarkers^{50, 51}, on AAA growth and rupture. A recent
4 study of Yamaguchi *et al.*⁵² demonstrated that periaortic adipose tissue was an independent
5 significant predictor for AAA progression. Additionally, flow-mediated dilation has shown to
6 have a weak but significant inversed correlation with future AAA progression⁵³. A recent review
7 of literature by Siasos *et al.*⁵⁴ highlighted the contribution of endothelial cells due to increased
8 oxidative stress to AAA development. This emphasizes a potential role of measures of
9 endothelial function and arterial stiffness in predicting AAA growth and rupture.

10 In conclusion, current measures of local vascular characteristics of the aortic wall have potential
11 to predict AAA growth, especially measuring metabolism and calcification. This implies that
12 those measures best represent the processes in the aortic wall, which leads to AAA progression.
13 AAA rupture demonstrated no convincing relation with one of the found measures. Although
14 more work is needed, metabolism could potentially be related to AAA rupture, since slightly
15 more metabolic active AAAs were found among ruptured AAAs than non-ruptured AAAs. This
16 emphasizes the role of aortic wall characteristics in AAA progression and therefore could
17 improve prediction of AAA growth and rupture through evaluation of these characteristics.

18

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4

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6 None.

7

8 **Data availability statement**

9 Not applicable.

10

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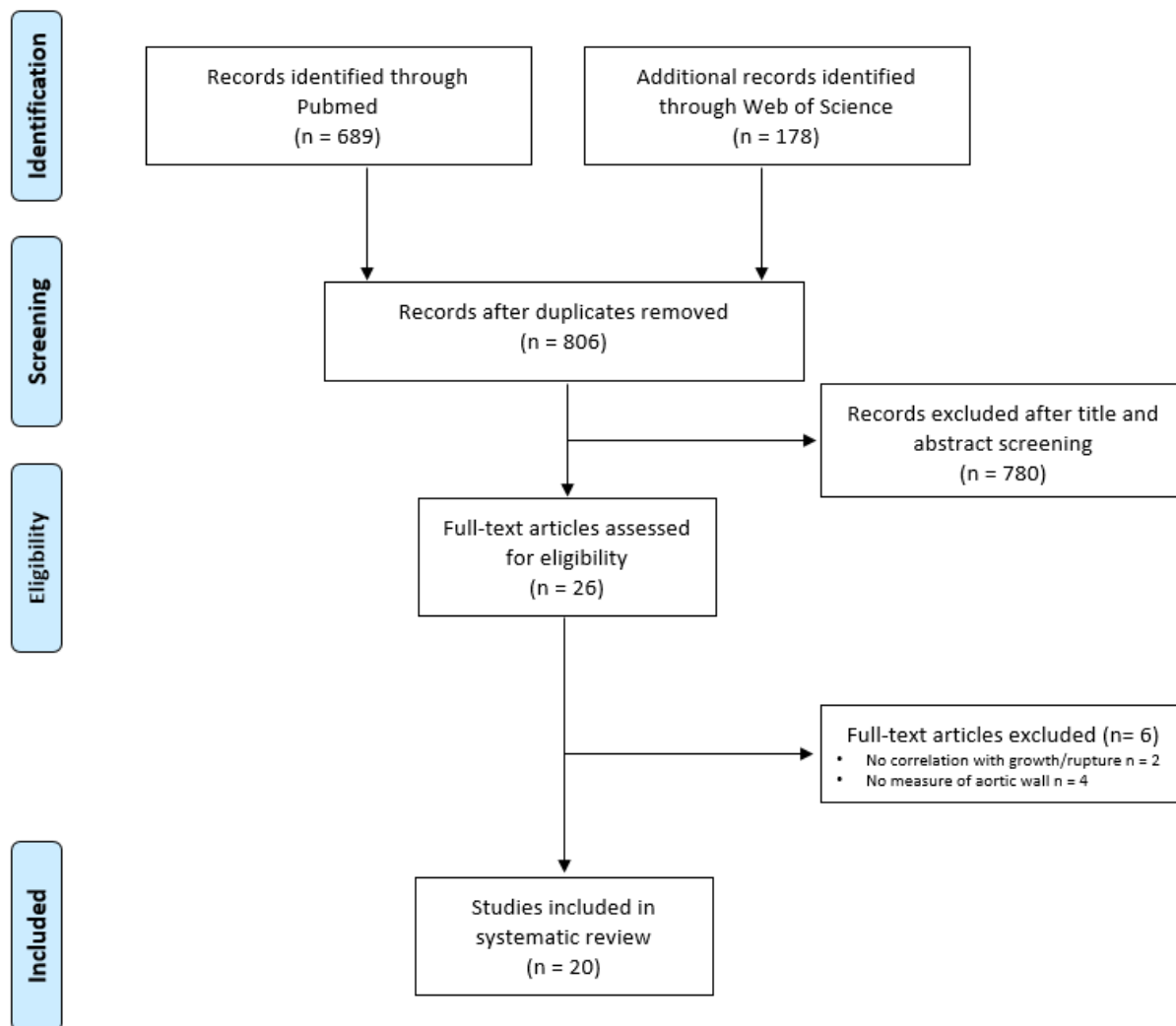
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1 **Figure legends**

2 *Figure 1.* Flowchart describing the inclusion of eligible studies

3

1 **Figures and Tables**

2

3 Figure 1.

4

Table I. Details included studies with regard to metabolism of aortic wall as measuring type*

Author Year	Study design (FU in months)	N	Measuring type (Technique)	Outcome		Main findings on association with growth/rupture
				Growth	Rupture	
Kotze 2011	Prospective cohort (12)	34	18F-FDG SUV _{max} (18F-FDG-PET/CT)	Aneurysm diameter	-	Inverse correlation between whole vessel 18F-FDG SUV _{max} and ultrasound expansion at 1 year (r=-0.50; P=0.01)
Richards 2011	Prospective cohort (6)	29	USPIO uptake in the aortic wall (USPIO- enhanced MRI)	Aneurysm diameter	-	Patients with distinct focal areas of increased USPIO uptake had 3-fold higher aneurysm growth rates compared to patients with no or nonspecific USPIO uptake (P=0.02)
Kuzniar 2019	Retrospective cohort (ND)	15	Aneurysm wall LGE and TBR _{max} , FDG hotspots (SUV _{max}) (18F-FDG- PET/MRI)	Aneurysm diameter	-	Significantly higher growth rates in LGE positive compared to LGE negative aneurysms (7 mm/yr vs 2 mm/yr; p=0.03). Recent AAA growth was positive correlated with number of FDG hotspots (r=0.62; P=0.013), but not with FDG hotspot SUV _{max} (r=0.198; P=0.48) or maximum TBR in the aneurysmal wall (r=0.406; P=0.13).
Forsythe 2018	Prospective cohort (17)	72	18F-NaF SUV _{max} (18F- NaF-PET/CT)	Aneurysm diameter	Confirmed by autopsy.	Higher expansion rate in tertile 3 of 18F-NaF-uptake in AAA patients (3.10 mm/yr), compared to tertile 1 (1.24 mm/year) and tertile 2 (1.55 mm/yr) (P=0.008). No significant difference in rupture events between tertile 1 (1/24), tertile 2 (2/24) and tertile 3 (0/24).

Forsythe 2018	Prospective cohort (33.5)	342	USPIO enhancement in aneurysm wall (<i>USPIO- enhanced MRI</i>)	Aneurysm diameter	Confirmed by clinical end point committee	USPIO enhanced versus non-USPIO enhanced aneurysm shows higher aneurysm growth rates (3.1 ± 2.5 mm/yr vs 2.5 ± 2.4 mm/yr, P=0.04) and more events of rupture (10/146 vs 7/191, P=0.19).
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* FU = follow-up, N = sample size, ND = not determined, SUV = standardized uptake value, LGE = late gadolinium enhancement, TBR = target to background ratio

Table II. Details included studies with regard to calcification as measuring type*

Author Year	Study design (FU in months)	N	Measuring type (<i>Technique</i>)	Outcome		Main findings on association with growth/rupture
				Growth	Rupture	
Lindholt 2008	Prospective cohort (73.8)	122	Degree of calcification (B-mode-ultrasonography)	Aneurysm diameter	-	Patients with AAA wall calcification (i.e. >50%) show lower growth (1.72 mm/yr vs 2.97 mm/yr; P=0.001).
Hendy 2015	Retrospective cohort (16)	88	Infrarenal aortic calcification volume (CT)	Aneurysm diameter and volume	-	Above <i>versus</i> below median calcification: No differences in diameter (1.8 mm/yr versus 1.6 mm/yr, P=0.99) or volume (7.8 cm ³ /yr versus 6.0 cm ³ /yr, P=0.66)
Nakayama 2016	Retrospective cohort (19.2)	414	Percentage of calcification, (CT)	Aneurysm diameter	-	Calcification is inversely related with AAA expansion.
Siegel 1994	Retrospective case-control (ND)	108	Thrombus size + calcification (CT)	-	Confirmed by clinical course, surgery, or autopsy.	Focal discontinuity in circumferential calcification was seen in 8% of ruptured aneurysms. Significantly lower amount of thrombus (2.04 vs 2.29; P=0.01) and thrombus calcification (13% vs 25%; P=0.01) in ruptured AAAs compared to non-ruptured AAAs.
Buijs 2013	Retrospective case-control (ND)	334	Abdominal Aortic Calcification-8 score (CTA)	-	Confirmed by CTA or surgery	Significant higher AAC-8 scores in patients with symptomatic (P<0.05) and ruptured AAA (P<0.05) compared to elective AAA.

* FU = follow-up, N = sample size, ND = not determined, CTA = computed tomography angiography

Table III. Details included studies with regard to intraluminal thrombus as measuring type*

Author Year	Study design (FU in months)	N	Measuring type (Technique)	Outcome		Main findings on association with growth/rupture
				Growth	Rupture	
Speelman 2009	Retrospective cohort (9)	30	ILT volume (CTA)	Aneurysm diameter	-	Above versus below median ILT volume: Significantly higher growth rate in AAAs above median ILT volume (above: 3 (1-6) mm, below: 0 (0-1.2) mm; P<0.01).
Metaxa 2015	Retrospective cohort (11.5)	34	ILT volume, thickness and deposition (CT)	Aneurysm diameter	-	Significantly lower growth rate in AAAs with posterior versus anterior thrombus deposition (mean -0.032 vs 0.336, p=0.035). No difference in ILT volume (36 mL vs 35 mL; P=0.62) or ILT thickness (14.4 mm vs 12.5 mm; P=0.57) between high and low growth rate AAAs
Domonkos 2019	Retrospective cohort (24)	26	Relative ILT size (CTA)	Aneurysm diameter	-	Negative correlation between relative ILT size at baseline and aneurysm growth (r=-0.32; P=0.04)
Zhu 2019	Prospective cohort (16)	41	ILT subtype, ILT area change, ILT volume change, baseline ILT volume, ILT thickness change (MRI)	Aneurysm diameter	-	Significantly higher growth rates in AAAs with bright ILT compared to AAAs with isointense ILT or no ILT (2.6 ±2.5 vs 0.6 ±1.3 vs 1.5 ±1.6 mm/yr; P = 0.01). 3-fold higher growth rate in AAAs with active ILT changes compared to AAAs with stable ILT (3.6 ±3.0 mm/yr vs. 1.2 ±1.3 mm/yr; P = 0.008). AAA growth is not associated with ILT area (r=0.42, P=0.06) or ILT volume change (r = 0.09, P = 0.70), but has a moderate association with

						ILT thickness change ($r = 0.53$; $P = 0.02$) and baseline ILT volume ($r = 0.43$, $P = 0.05$).
Haller 2018	Retrospective case-control (<i>ND</i>)	51	ILT thickness, ILT % volume (<i>CTA</i>)	-	Confirmed by surgery	Significantly higher normalized ILT thickness and % volume ILT in small rAAA compared to large non-rAAA group (95% CI, 0.13-0.19 vs 0.10-0.13; $P < 0.01$ and 95% CI, 59.6%-77.2% vs 50.2%-63.1%; $P = 0.02$) and small non-rAAA (95% CI, 0.13-0.19 vs 0.08-0.13; $P < 0.01$ and 95% CI, 59.6%-77.2% vs 42.9%-62.2%; $P = 0.02$).

* FU = follow-up, N = sample size, ND = not determined, CTA = computed tomography angiography, rAAA = ruptured abdominal aorta aneurysm

Table IV. Details included studies with regard to compliance as measuring type*

Author Year	Study design (FU in months)	N	Measuring type (Technique)	Outcome		Main findings on association with growth/rupture
				Growth	Rupture	
Wilson 1999	Prospective cohort (21)	60	Compliance (parameters E_p and β) (<i>Ultrasonic echo-tracking</i>)	Aneurysm diameter	-	No relationship between growth rate and E_p ($r=-0.09$) or β ($r=-0.13$) at the end of follow up.
Vonk 2014	Prospective cohort (48)	7	Compliance, distensibility, E_{inc} (<i>2D ultrasound elastography</i>)	Aneurysm diameter	-	Higher relative increase in E_{inc} for patients with fast growth aneurysms (75%-700%) compared to medium (25%-125%) and no growth aneurysms (-10%-100%).
Lorenzen 2021	Retrospective cohort (12)	326	Wall stiffness (<i>Ultrasound</i>)	Aneurysm diameter	-	Baseline wall stiffness does not predict growth rate ($P=0.32$). No correlation between change in wall stiffness and growth rate ($r=0.053$, $P=0.38$).
Sonesson 1999	Retrospective cohort (ND)	132	Wall stiffness (<i>Ultrasonic echo-tracking</i>)	-	Confirmed by autopsy, emergency surgery and clinically	No difference in aneurysmal wall stiffness in those AAAs that subsequently ruptured compared with electively operated AAAs.
Wilson 2003	Prospective cohort (19)	210	AAA distensibility (parameters E_p and β) (<i>Ultrasonic echo-tracking</i>)	-	Death certificate information from the NHS or hospital records.	Significant association between D_{max} ($P=0.002$), change in E_p ($P=0.011$), diastolic BP ($P=0.004$) and time to rupture.

						No statistically significant difference in baseline E_p (2.61 N/m ² vs 2.93 N/m ² ; P=0.244) or β (16.5 AU vs 19.8 AU; P=0.116) between ruptured and non-ruptured AAAs
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* FU = follow-up, N = sample size, ND = not determined, E_p = pressure strain elastic modulus, β = stiffness, E_{inc} = incremental Young's modulus, NHS = national health service, D_{max} = maximum anterior-posterior AAA diameter, BP = blood pressure

Supplemental Tables

Supplemental Table I. Search strategy for all databases

Database	Search terms
PubMed	<p>((aortic aneurysm, abdominal[mesh terms]) or (abdominal aort* aneurysm*[tw]) or (AAA[tw]) or (AAAs[tw]) or (aortic abdominal aneurysm[tw])) AND ((disease progression[mesh terms]) or (aneurysm, ruptured[mesh terms]) or (aortic rupture[mesh terms]) or (prognosis[mesh terms]) or (rupture risk[tw]) or (predict*[tw]) or (progress*[tw]) or (grow*[tw]) or (expan*[tw]) or (rupture*[tw])) AND ((vascular[tw]) or (wall[tw])) AND ((biomechanical phenomena[mesh terms]) or (wall stress[tw]) or (shear stress[tw]) or (biomechanic*[tw]) or (compliance[mesh]) or (stiff*[tw]) or (stress*[tw]) or (pulse wave velocity[tw]) or (wall tension[tw]) or (calcification[title/abstract]) or (inflammation[mesh terms]) or (immune system phenomena[mesh terms]) or (18F-FDG[tw]) or (inflammation[tw]) or (oxidative stress[mesh terms]) or (reactive oxygen species[mesh terms]) or (biomarkers[tw])) NOT ((endovascular procedures[mesh terms]) (endovascular repair[tw]) or (treatment outcome[mesh terms]) or (postoperative[title/abstract]) or (surgery[title]) or (surgical repair[title]) or (EVAR[title]) or (graft[tw])) NOT ((Animals[Mesh terms]) not (humans[mesh terms])) not (mice[tw]))</p>
Web of Science	<p>((abdominal aortic aneurysm AND (growth OR rupture)) AND (vascular OR wall) AND (biomechanical OR stress* OR compliance OR stiff* OR pulse wave velocity OR wall tension OR calcification OR inflammation OR 18F-FDG OR oxidative stress OR reactive oxygen species OR biomarkers) NOT (treatment OR therapy OR repair OR surgery OR mice OR animal OR models))</p>

Supplemental Table II. Quality assessment of included studies*

Risk of bias assessment using the Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I) tool								
Study	Risk of bias pre- and at-intervention domains			Risk of bias post-intervention domains				Overall assessment of bias
	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended intervention	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	
Siegel 1994	Low	Moderate	Low	NI	Low	Low	Low	Moderate
Sonesson 1999	Serious	Low	Low	NI	Low	Low	Low	Serious
Wilson 1999	Serious	Moderate	NI	NI	Low	Low	Low	Serious
Wilson 2003	Low	Moderate	Low	NI	Low	Low	Low	Moderate
Lindeholt 2008	Moderate	Low	Low	NI	Low	Low	Low	Moderate
Speelman 2010	Low	Low	Low	NI	Low	Low	Low	Low
Kotze 2011	Moderate	Low	NI	NI	Moderate	Low	Low	Moderate
Richards 2011	Low	Low	Low	NI	Moderate	Low	Low	Moderate
Buijs 2013	Low	Low	Low	NI	Low	Moderate	Low	Moderate
Vonk 2014	Serious	NI	Serious	NI	Low	Low	Low	Serious
Hendy 2015	Low	Serious	Low	NI	Low	Low	Low	Serious
Metaxa 2015	Serious	Low	Low	NI	Low	Low	Low	Serious
Nakayama 2016	Low	Moderate	NI	NI	Low	Low	Low	Moderate
Forsynthe 2018	Low	Low	Low	NI	Low	Low	Low	Low
Forsynthe 2018	Low	Low	Low	NI	Low	Low	Low	Low
Haller 2018	Low	Low	Low	NI	Low	Serious	Low	Serious
Domonkos 2019	Serious	Moderate	Low	NI	Low	Moderate	Low	Serious
Zhu 2019	Moderate	Low	Low	NI	Moderate	Low	Low	Moderate
Kuzniar 2020	Moderate	Low	Low	NI	Low	Low	Low	Moderate
Lorenzen 2021	Low	Moderate	NI	NI	Low	Low	Low	Moderate

* NI = No information; Low = Low risk of bias; Moderate = Moderate risk of bias; Serious = Serious risk of bias; Critical = Critical risk of bias

