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SYSTEMATIC REVIEW

Systematic Review of the Co-Prevalence of Arterial Aneurysms Within the Vasculature

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WHAT THIS PAPER ADDS

Arterial aneurysms are mostly treated as solitary vascular pathologies, although concomitant aneurysmal disease is reported in various arterial beds. This study gives an overview of the reported co-prevalence of aneurysms in different vascular territories, and may facilitate doctor to patient information and consideration for screening of other arterial beds beyond the primary aneurysm. Future consideration of the health related burden, when the concomitant aneurysm at screening is left untreated, should be performed for clinical implementation of additional screening algorithms.

Objective: Aneurysms are considered focal manifestations of a systemic vascular condition, and various studies report co-prevalence of aneurysms in different vascular beds. Insight into profiles of patients at risk of multiple aneurysms is lacking, and few clinical algorithms exist if additional screening is indicated. This systematic review assessed the co-prevalence of aneurysms in different vascular beds and analysed putative risk factors for multiple aneurysms.

Methods: Medline, Embase, and Cochrane libraries were searched up to February 2020 for studies reporting co-prevalence of aneurysms in different vascular beds using the keywords: "aneurysm", "co-prevalence", or synonyms. All studies were reviewed by two authors independently. Studies were excluded if they described concomitant treatment of multi-aneurysms, or if the aneurysm was reported solely bilateral, post-dissection, mycotic, traumatic, iatrogenic, or caused by a connective tissue disease. Radar plots were used to indicate studies that found an association between the investigated features and aneurysm co-prevalence against those that did not.

Results: Thirty-two studies met the inclusion criteria, describing in total 16 353 patients of whom 2 015 had at least one additional aneurysm. The weighted co-prevalence was 16.9% (95% confidence interval [CI] 11.8–22.6), $I^2 > 90\%$. At least 19 combinations of aneurysms were described, mostly derived from retrospective studies. Seventeen of 32 (53%) studies described concurrent aneurysms in patients with an abdominal aortic aneurysm. Predominantly positive associations were found for higher age, hypertension, stenotic disease, presence of multiple (at least three) aneurysms, and primary aneurysm size.

Conclusion: Approximately one in six patients with a primary aneurysm harbours an additional aneurysm, increasing to one in four if the patient has a popliteal artery aneurysm. Higher age, hypertension, stenotic disease, presence of multiple (at least three) aneurysms, and primary aneurysm size were predictive of aneurysm co-prevalence. These clinical predictors may assist when deciding whether a patient with a primary aneurysm needs to be screened for additional aneurysms.

Keywords: Additional, Aneurysm, Concurrent, Co-prevalence, Review
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INTRODUCTION

Aneurysmal dilatations in arterial beds are mostly focal manifestations of a systemic vascular condition, and

numerous studies have reported co-prevalence of aneurysms in different arterial beds.[1–4] Although the site of an aneurysm is likely to be subject to anatomical initiating factors, the systemic propensity is determined by environmental and genetic factors.[1,5] A genetic overlap was suggested in aortic aneurysms (AA) and associated with intracranial aneurysms,[6] and peripheral aneurysms.[7,8] In general, aneurysm risk includes higher age, smoking, and sex, but genetic susceptibility, inflammation status, and haemodynamics may also contribute to aneurysm disease.[1] In general, aneurysms are defined as dilatations $\geq$ 150% compared with the proximal non-affected part of the artery, but diameter thresholds, for example abdominal aortic aneurysms (AAA) $\geq$ 30 mm, have been used and applied widely.[1,9,10]

The updated clinical practice guideline for the management of AAA from the European Society for Vascular Surgery (ESVS) states that screening at 5—10 year intervals for AAA may be considered for all men and women with a true peripheral arterial aneurysm (IIb, level C).[9] The American SVS guideline for AAA also recommends evaluation for an AAA, although only in patients with a popliteal or femoral artery aneurysm.[10] Physical examination that includes the femoral and popliteal arteries is also recommended in patients with a suspected or known AAA (1, level A).[10] The ESVS 2020 guideline for acute limb ischaemia is more directive, stating that screening of the treated and contralateral arteries every three years should be considered in patients treated for a thrombosed popliteal aneurysm with duplex ultrasound imaging, as well as screening of the aorta, iliac, and femoral arteries (IIa, level C).[11]

As the different guidelines vary and/or lack insights into the risk profile for patients at risk of concurrent aneurysms, and with exception of the latter,[11] type and extensiveness of aneurysm evaluation is left to the readers' interpretation. Therefore, clinical implementation of these recommendations can vary among treating physicians. The present systematic review was undertaken to give an overview of available evidence of co-prevalence of aneurysms in the vasculature, and potentially indicate putative clinical risk factors for concurrent aneurysm disease.

METHODS

Search strategy and selection criteria

This systematic review and meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[12] Medline, Embase, and Cochrane Library databases were systematically searched to identify all studies published until 27 February 2020 which described a co-prevalence of aneurysms in different vascular beds in patients aged $\geq$ 18 years. The keywords "aneurysm" and "co-prevalence", and their synonyms, were used in the search to select the studies for this review (the full search is listed in Table S1). The search results were recorded in an electronic database (The EndNote team 2013. EndNote X9, Clarivate Analytics, Philadelphia, PA, USA) and duplicates were removed. All articles were screened based on title and abstract by two independent observers (CL, NJ), according to predefined inclusion and exclusion criteria. Afterwards, the full text of eligible studies was screened to determine its appropriateness for this systematic review (excluded studies after full text screening are listed in Table S2). Additional articles were identified by cross linking. The review was restricted to English language studies. Disagreements were discussed until consensus was reached. All studies describing original research of co-prevalence of at least two aneurysms were eligible for this review. Studies were excluded when reporting on case series ($\leq$20); case reports only; patients aged $\leq$ 17 years; intervention research reporting concomitant treatment of multiple aneurysms; in case of solely bilateral disease (e.g. bilateral popliteal artery aneurysm); or if the aneurysm was mycotic, iatrogenic, post-dissecting, or caused by a connective tissue disease.

Data extraction and assessment of methodological quality

The primary outcome measure was the reported co-prevalence of at least two aneurysms, secondary outcome was the availability of putative clinical risk features for co-prevalence. Data extracted included: study design, study period, number of patients, type of primary and concurrent aneurysm, co-prevalence ratio, the definition used for aneurysms, imaging modality, and availability of uni- and/or multivariable regressed patient related risk factors for co-prevalence. To obtain all adjusted results, both significant and non-significant risk estimates, corresponding authors were contacted for additional data. Included studies were assessed for quality by a modified risk of bias tool for prevalence studies.[13] Articles were assessed on Directness of Evidence (DoE) (0—4 points) in Table 1, and Risk of Bias (RoB) (0—8 points) in Table 2. Detailed scoring criteria are listed in Table S3. The DoE indicates to what extent the study matches the primary research question and the RoB indicates whether the study methodology contained risk of bias. Studies with high DoE (3.5—4 points) and low RoB (6—8 points) were most eligible for the present review. Two authors (CL, NJ) independently assessed methodological quality and carried out data extraction from the individual papers.

Statistical analysis

The overall co-prevalence was estimated using a random effects model with double arcsine transformation.[14] Weighted means with 95% confidence interval (CI) of the proportion of patients with aneurysm co-prevalence were calculated using MetaXL 5.3 [14] (Epigear International Pty Ltd 2011, Sunrise Beach, Queensland, Australia; www.epigear.com). The percentage of variability in estimates

Table 1. Quality assessment as directness of evidence of 32 studies reporting the co-prevalence of aneurysms in different vascular beds

Study (year)	Directness of evidence[†]				
	Outcome*				Total (score)
	Domain	Determinant	Co-prevalence	Patient characteristics	
Laukka (2019)	+	+	+	−	Moderate (3)
Goyal (2015)	+	+	+	≠	High (3.5)
Malhotra (2019)	+	+	+	≠	High (3.5)
Kuzmik (2010)	+	+	+	≠	High (3.5)
Erben (2020)	+	+	+	≠	High (3.5)
Miyazawa (2007)	+	+	+	≠	High (3.5)
Kurtelius (2019)	+	−	+	+	Moderate (3)
Lee (2017)	+	+	+	+	High (4)
Rouchaud (2016)	+	+	+	+	High (4)
Shin (2015)	+	−	+	≠	Moderate (2.5)
Hill (2019)	+	+	+	≠	High (3.5)
van Laarhoven (2020)	+	+	+	+	High (4)
Endo (2019)	+	+	+	+	High (4)
Stajduhar (1993)	+	+	+	−	High (3)
Balderston (2015)	+	+	+	+	High (4)
DeFreitas (2016)	+	+	+	+	High (4)
Dombrowski (2020)	+	+	+	≠	High (3.5)
Wallinder (2018)	+	−	+	−	Low (2)
Hultgren (2012)	+	+	+	+	High (4)
Chaer (2012)	+	+	+	+	High (4)
Chapman (2017)	+	+	+	+	High (4)
Hohneck (2019)	+	−	+	−	Low (2)
Studziński (2019)	+	+	+	≠	High (3.5)
Armon (1998)	+	−	≠	−	Low (1.5)
Dent (1972)	+	+	+	−	High (3)
Laine (2017)	+	−	≠	−	Low (1.5)
Graham (1980)	+	−	+	−	Low (2)
Cervin (2020)	+	+	+	≠	High (3.5)
Tuveson (2016)	+	−	+	+	Moderate (3)
Diwan (2000)	+	+	+	≠	High (3.5)
Ravn (2017)	+	−	+	−	Low (2)
Ravn (2008)	+	+	+	+	High (4)

* + equals 1 point; ≠ equals 0.5 points; - equals 0 points.
† Directness of Evidence score: Low (0−2); Moderate (2.5−3); High (3.5−4). Full definitions are given in Table S3.

attributable to interstudy heterogeneity was quantified by the I^2 statistic (%). The higher the I^2 statistic percentage, the more observed interstudy heterogeneity rather than by chance alone.[15] As a rough reference, I^2 of 30%−60% represents moderate heterogeneity, 50%−90% substantial heterogeneity, and 75%−100% considerable heterogeneity.[15] All associated clinical risk features were collected from the separate articles. If a putative feature was reported in fewer than six articles, this feature was excluded from further analysis. A semi-quantitative analysis was performed by plotting studies that found an association between the investigated features and co-prevalence of aneurysms against those that did not find an association. The results with total number of investigated patients are shown in radar graphs. Corresponding authors of included studies that reported adjusted odds ratios (OR) for different patient features were approached and asked to send additional data on all included variables. Obtained data were assessed by meta-analysis using Review Manager (version 5.3.5; Nordic Cochrane Centre, Copenhagen, Denmark). A random effects model (Mantel-Haenszel method) was used to account for the heterogeneity in the included observational cohort studies.

RESULTS

Study selection

The search identified 7 213 unique articles. After excluding 7 187 articles and adding six articles[3,16−20] by cross linking, 32 original research articles met the inclusion criteria (Fig. 1, Table S4). Results of the quality assessment of these 32 studies are presented in Tables 1 and 2. In total, eight studies[19,21−27] (22%) were assessed as having a high risk of bias in reporting co-prevalence of aneurysms.

Study sample

The study characteristics are summarised in Table 3. In total 16,353 study patients were included, of whom 2 015 had at least one additional aneurysm, representing an overall weighted co-prevalence of 16.9% (95% CI 11.8−22.6). Most articles described post-hoc analyses in retrospective cohort studies, and only six studies[2,3,28−31] (19%) were conducted in a prospective manner. Predominately cohorts from Europe (41%) or the United States (47%) were described. In 21/32 (66%) articles, AA was described as the primary diagnosed aneurysm, and in 13/21 (62%) articles abdominal AA (AAA) in particular. Concurrent aneurysms were found in

Table 2. Quality assessment of risk of bias of 32 studies reporting the co-prevalence of aneurysms in different vascular beds

Study (year)	Risk of bias*								
	Sampling frame	Random selection and in-/exclusion	Aneurysm definition	Imaging modality	Consistent data collection	Reproducibility	Incomplete patient data	Co-prevalence and 95% CI	Total (score)†
Laukka (2019)	+	+	≠	−	−	+	−	+	Moderate (4.5)
Goyal (2015)	+	≠	≠	−	−	−	n/r	+	High (3)
Malhotra (2019)	+	+	−	+	−	−	−	+	Moderate (4)
Kuzmik (2010)	+	≠	−	−	−	−	n/r	+	High (2.5)
Erben (2020)	+	+	≠	+	+	−	n/r	+	Moderate (5.5)
Miyazawa (2007)	+	+	+	+	−	−	n/r	+	Moderate (5)
Kurtelius (2019)	+	+	−	−	−	≠	+	+	Moderate (4.5)
Lee (2017)	+	+	−	+	−	+	+	+	Low (6)
Rouchaud (2016)	+	+	≠	+	−	≠	n/r	+	Moderate (5)
Shin (2015)	+	+	≠	−	−	−	n/r	+	High (3.5)
Hill (2019)	−	+	≠	−	−	−	−	+	High (2.5)
van Laarhoven (2020)	+	+	≠	+	−	≠	+	+	Low (6)
Endo (2019)	+	+	≠	+	+	≠	n/r	+	Low (6)
Stajduhar (1993)	−	≠	≠	+	+	≠	−	+	Moderate (4.5)
Balderston (2015)	+	≠	+	+	+	≠	−	+	Low (6)
DeFreitas (2016)	+	+	+	+	+	−	n/r	+	Low (6)
Dombrowski (2020)	+	+	+	−	+	−	n/r	+	Moderate (5)
Wallinder (2018)	−	+	+	−	−	−	−	+	High (3)
Hultgren (2012)	+	+	+	+	−	+	n/r	+	Low (6)
Chaer (2012)	+	+	+	−	−	−	n/r	+	Moderate (4)
Chapman (2017)	−	+	+	+	+	+	n/r	+	Low (6)
Hohneck (2019)	−	+	+	+	+	+	−	+	Low (6)
Studziński (2019)	+	+	+	+	+	≠	+	+	Low (7.5)
Armon (1998)	+	+	≠	+	+	−	n/r	+	Moderate (5.5)
Dent (1972)	+	+	−	−	−	−	n/r	+	High (3)
Laine (2017)	−	+	+	−	+	−	+	+	Moderate (5)
Graham (1980)	−	+	+	−	−	−	n/r	+	High (3)
Cervin (2020)	−	≠	+	+	+	−	−	+	Moderate (4.5)
Tuveson (2016)	+	+	+	−	−	+	+	+	Low (6)
Diwan (2000)	+	+	≠	+	+	−	+	+	Low (6.5)
Ravn (2017)	−	≠	−	−	−	−	−	+	High (1.5)
Ravn (2008)	+	+	+	−	−	≠	+	+	Moderate (5.5)

* + equals 1 point; ≠ equals 0.5 points; - equals 0 points; n/r = not reported.
† Risk of bias score: High (0−3.5); Moderate (4−5.5); Low (6−8). Full definitions are given in Table S3.

various studied vascular beds, and more than 19 different combinations of aneurysm co-prevalence were reported. Fifteen studies (47%) defined both primary and concurrent aneurysms, in contrast to six studies[19,22,27,28,32,33] (19%) which did not define any of the studied aneurysms. The remaining 11 (34%) studies defined either only primary,[23,34] or concurrent aneurysm[3,16,20,21,25,29,35−37] (Supplementary material).

The weighted co-prevalence of intracranial aneurysm (IA) and thoracic aortic aneurysm (TAA) was 6.3% (95% CI 4.5−8.35) with I^2 = 55%, and for IA and AA (TAA, AAA, or combination of both, within one patient) was 9.3% (95% CI 3.0−8.1) with I^2 = 98%. Coronary artery aneurysms additional to AA disease were investigated in three studies, weighted co-prevalence was 22.6% (95% CI 19.0−26.5), I^2 = 16%. TAA and AAA were concurrently observed in 24.5% (95% CI 20.9−28.3), although I^2 was 76%. For common iliac artery and popliteal aneurysms, co-prevalence of 19.7% (95% CI 3.9−41.9) and 25.4% (95% CI 4.0−54.6) were found, respectively. The heterogeneity between these studies was considerable[15] ($I^2 > 98\%$), and, because of the small sample sizes, wide 95% CIs were observed. The highest co-prevalence (85/100) of 85% was observed in patients with common femoral artery aneurysm with concurrent AAA (RoB = 4, Table 2).[26] In 14 studies (44%) only one imaging modality was used, while in the remaining 18 studies multiple imaging modalities and types of scanners were used to confirm the diagnosis of the concurrent aneurysm (Supplementary material).

Putative clinical risk factors

In total, 20/32 studies described clinical risk factors for co-prevalence of aneurysms. An overview of the reported putative clinical risk factors is provided in Tables 4 and 5, more detailed information on the individual study results can be found in the Supplementary Material. In total, 19 studies described univariable regressed odds ratios (Table 4), and 10 unique patient cohorts reported multivariable adjusted risk estimates for multiple aneurysms (Table 5). Three corresponding authors[2,34,38] were able to send additional data, and one article[39] reported both significant and non-significant odds ratios. Pooled data from these four studies[2,34,38,39] (2 028 patients, 12% of total study population) are illustrated in Figs. S1A−D.

The relationship between studies reporting significant and not-significant risk estimates is illustrated in Fig. 2. For

higher age, hypertension, stenotic disease, presence of multiple (at least three) aneurysms, and primary aneurysm size, only positive or no associations were found throughout all studies. Only one positive association was found for chronic obstructive pulmonary disease (COPD),[17] but this was contradicted by adjusted results.[39,40] Family history of aneurysms was only positively associated once,[40] and no further associations were found. For male sex, smoking, and location of primary aneurysm, positive, negative, and non-significant associations were found. Male sex was only negatively associated with patients harbouring an AA or AAA, and co-prevalence of an IA[32,34] or TAA,[39,40] respectively. Both positive and negative risk estimates were observed for higher age, male sex, hypertension, and smoking when pooling crude estimates from obtained additional data (Figs. S1A—D). For diabetes mellitus, only one negative[40] and no further associations were reported, and for hyperlipidaemia only one large study[33] found a positive association while using a competing risks multivariable Cox regression model consisting of 4 378 patients (Table 5, Fig. 2B). For higher age, four of seven studies showed a positive association with aneurysm co-prevalence after multivariable regression analysis (Table 5). However, these studies represented a small number of patients (1 377 patients[2,17,39,41] *vs.* 1 584 patients[32,36,38]) (Fig. 2B). Location of the primary aneurysm showed a significant association in two studies, although in 1 082 patients[40] negative, and in only 462[17] patients positive odds. After adjustment, only COPD showed no association throughout (two of two studies[39,40]).

DISCUSSION

This systematic review (32 studies, 16 353 patients) showed that approximately one in six patients with a primary aneurysm harbours a concurrent aneurysm, and one in four if the patient has a popliteal aneurysm. Various cardiovascular risk features were analysed in the included studies, although none of the individual characteristics showed an unambiguous risk effect. Only positive or no associations were found for higher age, hypertension, stenotic disease, presence of multiple (at least three) aneurysms, and primary aneurysm size. Female sex was associated with co-prevalence of AA or AAA in patients in 2/10 studies, where patients additionally harboured an IA or TAA, respectively. In total, $>$ 19 combinations of different aneurysm were described, but mostly derived from post-hoc analyses in retrospective cohort studies.

Additional aneurysm screening is recommended in different guidelines,[9—11] although the extensiveness and screening time intervals vary. Clinical implementation may therefore differ per treating physician. The evidence supporting these recommendations is included in this review.[2,3,26] Age $\geq$65 years, male sex, smoking, hypertension, atherosclerosis, ethnicity, and family history of AAA are well established clinical risk factors associated with presence of AAA.[42—46] Diabetes, in particular type 2 diabetes mellitus, seems to prevent development of AAA.[47] Despite comprehensive discussion of risk factors for AAA development and outcomes after treatment, no separate insight into a risk profile for concurrent aneurysms is given in the guidelines.

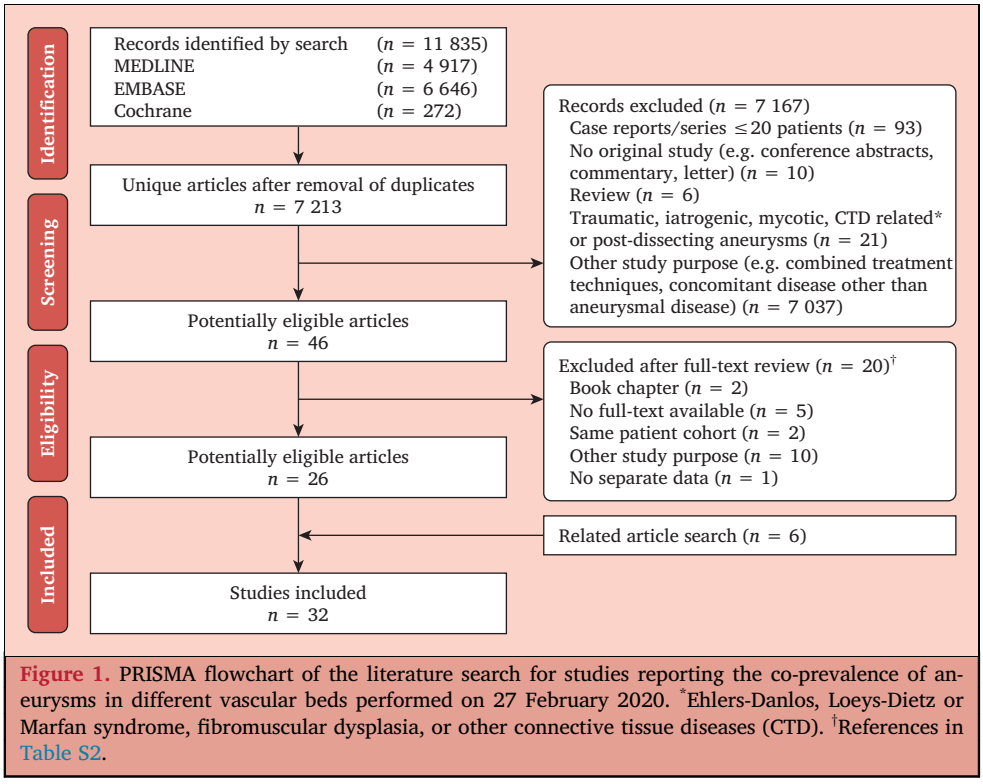

Figure 1. PRISMA flowchart of the literature search for studies reporting the co-prevalence of aneurysms in different vascular beds performed on 27 February 2020. *Ehlers-Danlos, Loeys-Dietz or Marfan syndrome, fibromuscular dysplasia, or other connective tissue diseases (CTD). †References in Table S2.

Table 3. Characteristics of 32 studies reporting the co-prevalence of aneurysms in different vascular beds

Study (year)	Study design	Study period – years	Sample size - *n*	Primary aneurysm	Concurrent aneurysm	Co-prevalence - %	CTD exclusion	Risk of bias (score)*
Laukka (2019)[35]	Re	2006–2016	411	sIA	TAA	7.5	No	Moderate (4.5)
Goyal (2015)[21]	Re	2002–2011	317	IA	TAA	4.7	No	High (3)
Malhotra (2019)[28]	P	6/2009–5/2018	554	TAA	IA	4.9	No	Moderate (4)
Kuzmik (2010)[22]	Re	1997–2009	212	TAA	IA	9.0	No	High (2.5)
							6.3 (4.5–8.35)§	
Erben (2020)[29]	P	8/2011–2/2014	81	IA	AAA	12.3	No	Moderate (5.5)
Miyazawa (2007)[18]	Re	9/1997–7/2003	181	IA	AAA	7.2	No	Moderate (5)
Kurtelius (2019)[33]	Re	1980–2014	4 378	sIA	AA	1.1	No	Moderate (4.5)
				fIA		14.0		
Lee (2017)[32]	Re	2009–2014	133	AA	IA	20.3	Yes	Low (6)
Rouchaud (2016)[34]	Re	1/2001–6/2015	1 081	AA	sIA	11.8	Yes	Moderate (5)
Shin (2015)[23]	Re	2005–2014	611	AA	sIA	11.6	Yes	High (3.5)
							9.3 (3.0–8.1)§	
Hill (2019)[25]	Re	2001–2016	31	RAA	IA	29	No	High (2.5)
van Laarhoven (2020)[36]	Re	2010–2016	1 082	IA	ECAA	3.2	No	Low (6)
Endo (2019)[37]	Re	1/2014–7/2017	123	AAA	CAA	27.6	No	Low (6)
Stajduhar (1993)[20]	Re	7/1986–10/1990	72	AAA	CAA	20.8	No	Moderate (4.5)
Balderston (2015)[38]	Re	1/2007–5/2013	477	AA	CAA	17	No	Low (6)
							22.6 (19.0–26.5)§	
DeFreitas (2016)[17] †	Re	2008–2013	462	TAA	AAA	22.5	No	Low (6)
Dombrowski (2020)[62]	Re	2007–2017	218	AAA	TAA	18.3	Yes	Moderate (5)
Wallinder (2018)[24]	Re	1982–2013	339	AAA	TAA and PAA‡	31.9	No	High (3)
Hultgren (2012)[39]	Re	2004–2008	354	AAA	TAA	26.6	Yes	Low (6)
Chaer (2012)[40]	Re	2000–2008	1 082	AAA	TAA	23.4	No	Moderate (4)
							24.5 (20.9–28.3)§	
Chapman (2017)[41] †	Re	2008–2013	371	TAA	CIAA‡	11.1	No	Low (6)
Hohneck (2019)[30]	P	2018–2019	40	AAA	CIAA‡	10	No	Low (6)
Studzińska (2019)[63]	Re	10/2017–7/2019	933	AAA	CIAA‡, VAA‡	31.7	No	Low (7.5)
Armon (1998)[16]	Re	6/1994–12/1996	215	AAA	CIAA	27.9	No	Moderate (5.5)
Dent (1972)[19]	Re	1960–1971	1 488	AAA	CFAA‡, VAA	3.9	No	High (3)
Laine (2017)[64]	Re	2002–2015	60	IIAA	AAA‡	41.7	No	Moderate (5)
Graham (1980)[26] †	Re	1956–1978	100	CFAA	AAA‡	85	No	High (3)
							19.7 (3.9–41.9)§	
Cervin (2020)[31]	P	2006–2017	145	AAA	PAA‡	15.9	No	Moderate (4.5)
Tuveson (2016)[65]	Re	2011–2013	225	AAA	PAA	19.1	No	Low (6)
Diwan (2000)[3]	P	1995–1998	313	AAA	PAA	11.5	No	Low (6)
Ravn (2017)[27] †	Re	1987–2012	74	PAA	AAA‡	23.4	No	High (1.5)
Ravn (2008)[2] †	P	1987–2002	190	PAA	AAA‡	68.9	No	Moderate (5.5)
						25.4 (4.0–54.6)§		
						16.9 (11.8–22.6)‖		

Re = retrospective; P = prospective; IA = intracranial aneurysm; sIA = saccular; fIA = fusiform; TAA = thoracic aortic aneurysm; AAA = abdominal aortic aneurysm; AA = aortic aneurysm; RAA = renal artery aneurysm; ECAA = extracranial carotid artery aneurysm; CAA = coronary artery aneurysm; PAA = popliteal artery aneurysm; CIAA = common iliac artery aneurysms; VAA = visceral artery aneurysm; CFAA = common femoral artery aneurysm; IIAA = internal iliac artery aneurysm.

* Risk of bias: High (0–3.5); Moderate (4–5.5); Low (6–8), see also Table S3.

† Overlapping inclusion periods, largest study sample included in weighted mean.

‡ Other branches.

§ Weighted mean (95% CI).

‖ Overall weighted mean (95% CI).

This review shows that pooling reliable risk estimates from the available co-prevalence studies is not straightforward. Applied imaging modalities, and definitions of included aneurysms and/or clinical risk features vary, resulting in heterogeneous study results (Supplementary material). To account for inherent differences, no direct comparisons of the included studies were made. However, based on this review, treating physicians should consider additional aneurysm screening in typical vascular patients (elderly male with hypertension and stenotic disease), and in the presence of multiple (at least three) aneurysms and large primary aneurysm size. In addition, female AA patients seem more susceptible to TAA or IA, and if they have IA they also have an increased risk of popliteal artery aneurysm.[23] Perhaps additional screening should be based on related health burden when the concurrent aneurysm at screening is left untreated. AAA screening in patients with an IA was reported to be cost effective in a American hypothetical cohort.[48] In addition to important financial aspects, quality of life in patients[49] harbouring multiple aneurysms, including aneurysms that do not require treatment, should be taken into account in additional screening guidelines. Although aneurysm rupture rate and hospital costs are subject to geographic location, similar simulation studies could be rewarding in selecting which artery should be screened additionally. Fairly benign concomitant

Table 4. Reported putative risk factors for co-prevalence of more than two aneurysms in univariable analysis of 32 studies reporting the co-prevalence of aneurysms in different vascular beds

Author (year)	*n*	High age	Male sex	Hyper tension	DM	Hyperlipi daemia	Stenotic disease	COPD	Smoking	Family history of aneurysms	Multiple aneurysms	Primary aneurysm size	Primary aneurysm location
Laukka (2019)[35]	411												
Goyal (2015)[21]	317	NS	+	+					NS				
Malhotra (2019)[28]	554	NS	NS	NS					m				NS
Kuzmik (2010)[22]	212	NS	NS	+					NS				+
Erben (2020)[29]	81	NS	NS	NS	NS	NS	NS		NS		NS		
Miyazawa (2007)[18]	181	+	+	NS	NS		NS		+	NS	+	+	NS
Kurtelius (2019)[33]	4 378												
Lee (2017)[32]	133	+	−	NS	NS	NS			NS				+
Rouchaud (2016)[34]	1 081	NS	−	NS	NS	NS	+		NS			+	
Shin (2015)[23]	611	NS	+	NS	NS	NS	NS		NS		NS		NS
Hill (2019)[25]	31												
van Laarhoven (2020)[36]	1 082	NS	+	NS	NS	NS			NS	NS			
Endo (2019)[37] †	123												
Stajduhar (1993)[20]	72												
Balderston (2015)[38]	403*	+	NS	NS	NS		NS		NS		NS	NS	
DeFreitas (2016)[17]	462	+	NS	+	NS		+	+	+	NS	NS		
Dombrowski (2020)[62]	218	NS	NS	NS	NS	NS		NS	NS	NS		NS	
Wallinder (2018)[24]	339												
Hultgren (2012)[39]	354	+	−	+	NS	NS	NS	NS	NS			NS	
Chaer (2012)[40]	1 082	+	−	+	−	NS		NS	−	+			+
Chapman (2017)[41]	371	+	+	+	NS		+	NS	NS	NS	+		
Hohneck (2019)[30]	40												
Studzińska (2019)[63]	933												
Armon (1998)[16]	215												
Dent (1972)[19]	1 488												
Laine (2017)[64]	60												
Graham (1980)[26]	100												
Cervin (2020)[31]	145*											NS	
Tuveson (2016)[65]	225	NS	NS		NS		+	NS	NS				
Diwan (2000)[3]	313	NS	+	NS	NS	NS	+		NS	NS			
Ravn (2017)[27]	74												
Ravn (2008)[2]	190	+	NS	+					NS	NS	+*		

DM = diabetes mellitus; COPD = chronic obstructive pulmonary disease; + = positive association with co-prevalence of aneurysms; - = negative association with co-prevalence of aneurysms; NS = not significant; m = missing data in >30% of patients.
* Subgroup analysis.
† Analysed propensity score matched cohort without aneurysm patients.

aneurysms at screening (e.g. coronary or extracranial carotid artery aneurysms) with low risk of adverse outcome will be excluded, and sophisticated screening recommendations for additional high risk aneurysms will subsequently be generated.

Of the six prospective studies, only one reported adjusted risk estimates,[2] probably partly because of the small number of events and thus statistical power.[3,28–31] Higher age and hypertension at baseline were independently associated with extra aneurysms in the Swedish analysis of 190 patients with popliteal artery aneurysms who were re-examined after a median of seven years.[2] Somewhat similar results were observed in the present meta-analyses, although the I^2 statistic was considerable for age and male sex (Figs. S1A and B). Presence of at least three aneurysms was observed in various studies. It seems logical that harbouring multiple aneurysms is associated with co-prevalence of even more arterial aneurysms, although the question remains when having either one aneurysm or more, whether all dilatations are caused by the same aneurysm prone vascular subtype. As connective tissue diseases such as Marfan and Ehlers-Danlos syndromes are rarely tested for and diagnosed,[50] it is reasonable to assume that these and other yet to be discovered genetic vascular types contribute to aneurysm development. A shared genetic base was shown in twin studies[51,52] and first grade relatives with AAA[53,54] and IA,[55] indicating that family history affects future aneurysm development. Future research should include first relative family history for other arterial aneurysm types. Some evidence has been raised that patients with an AAA have peripheral arteriomegaly,[56] this may explain why the size of the primary aneurysm is associated with co-prevalence of concurrent aneurysms, in particular when absolute values are used for aneurysm definition. Large aneurysm size also indicates advanced aneurysmal disease and contributing risk factors could have dilated other vascular territories simultaneously. Previous research has shown remarkable aneurysm development in

Table 5. Reported putative risk factors for co-prevalence of more than two aneurysms in multivariable regression analysis of 32 studies reporting the co-prevalence of aneurysms in different vascular beds

Author	*N*	High age	Male sex	Hyper tension	DM	Hyperlipi daemia	Stenotic disease	COPD	Smoking	Family history of aneurysms	Multiple aneurysms	Primary aneurysm size	Primary aneurysm location
Laukka (2019)[35]	411												
Goyal (2015)[21]	317												
Malhotra (2019)[28]	554												
Kuzmik (2010)[22]	212												
Erben (2020)[29]	81												
Miyazawa (2007)[18,†]	181												
Kurtelius (2019)[33]	4 378		+	NS	NS	+	+						
Lee (2017)[32]	133	NS	NS										NS
Rouchaud (2016)[34]	1 081		−				NS					NS	NS
Shin (2015)[23]	611												
Hill (2019)[25]	31												
van Laarhoven (2020)[36]	1 048[*]	NS	+	NS	NS	NS							
Endo (2019)[37 ‡]	123												
Stajduhar (1993)[20]	72												
Balderston (2015)[38]	403[*]	NS	NS	NS	NS		NS		NS		NS	NS	
DeFreitas (2016)[17]	462	+	+	+					+				+
Dombrowski (2020)[62]	218												
Wallinder (2018)[24]	339												
Hultgren (2012)[39]	354	+	−	NS	NS		NS	NS	NS				
Chaer (2012)[40]	1,082		NS	+	−	NS	NS	NS	−	+		+	−
Chapman (2017)[41]	371	+	+								+		
Hohneck (2019)[30]	40												
Studzińska (2019)[63]	933												
Armon (1998)[16]	215												
Dent (1972)[19]	1,488												
Laine (2017)[64]	60												
Graham (1980)[26]	100												
Cervin (2020)[31]	145[*]												
Tuveson (2016)[65]	225												
Diwan (2000)[3]	313												
Ravn (2017)[27]	74												
Ravn (2008)[2]	190	+	NS	+					NS	NS			

DM = diabetes mellitus; COPD = chronic obstructive pulmonary disease; + = positive association with co-prevalence of aneurysms; - = negative association with co-prevalence of aneurysms; NS = not-significant.

[*] Subgroup analysis.

[†] Adjusted for 12 covariates in <15 events.

[‡] Analysed propensity score matched cohort without aneurysm patients.

the autologous vein used as arterial bypass in the treatment of patients with popliteal aneurysms.[57] In addition, histopathological analysis of the inferior mesenteric vein[58,59] in AAA patients revealed fragmentation of elastin fibres of the venous tissue and elastin depletion within the venous medial layer. Taken together, this suggests that the vasculature may be systemically affected by the interplay of many inflammatory proteins and cytokines, such as matrix metalloproteinases (MMP, e.g. MMP2 or 9 [7,58,60]) and interleukin 6,[61] which have a pivotal role in aneurysm formation and progression.

Limitations and future perspectives

Because of the broad nature of the present research question, it is inevitable that other informative articles were missed, although extensive cross linking was performed to minimise this. Multiple aneurysms within the same artery were left out of this analysis in attempt to analyse aneurysmal disease in different vascular beds, although defining a cut off point between arteries is arbitrary and subject to the study properties. The influence of connective tissue diseases (CTD) on aneurysmal disease was minimised by excluding articles describing solely CTD related aneurysms, although it is possible that some patients with CTD remain in the present review, as genetic testing to confirm the diagnosis is subject to local practice. Further, the majority of included papers performed a post-hoc analysis in a retrospective database. Many of the study patients were selected from a surgically driven cohort, and associated risk features could have been taken care of (e.g. smoking cessation), and as a result their influence may be less pronounced. The timing of enrolment (first diagnosis or after surgery), and more importantly timing and indication for additional imaging of specific regions of interest,

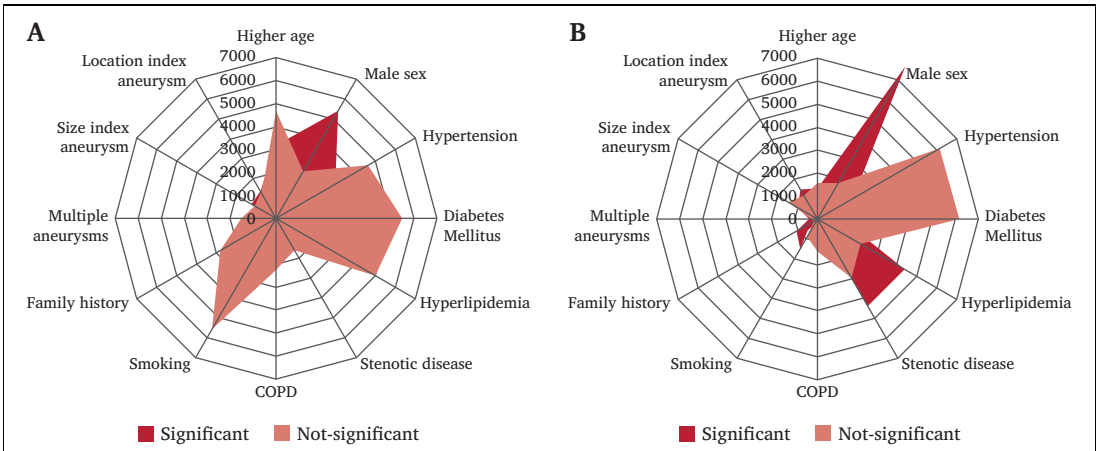

Figure 2. Radar graphs of the included univariable (A; 19 studies) and multivariable (B; 10 studies) regressed putative clinical risk features analysed in studies reporting co-prevalence of aneurysms based on the systematic literature review. Studies that found a significant association (dark coloured) were plotted against studies finding a non-significant association (light coloured). The y axis represents the cumulative number of study patients; each axis of the circular radar graph represents one clinical risk factor.

is not addressed in many studies and may contribute to selection bias. Moreover, in retrospective studies the time of diagnosis of both aneurysms could differ largely, and the cross sectional design for prevalence estimation may be violated. The difference in prevalence or incidence should therefore be emphasised, as the associated risk features may also be time dependent, for example recent infection, surgery, or arterial dissection. Only one prospective study included time to diagnosis in its analyses.[2] Even though retrospective co-prevalence studies are a reflection of daily clinical practice, associated aetiological results are hampered by this. Additionally, it was only possible to pool crude data from four studies despite extensive contact with corresponding authors. Because of the observed heterogeneity in the co-prevalence studies, pooling data by an individual patient data meta-analysis was not feasible. Future studies aiming to unravel concurrent aneurysmal disease should, ideally, be performed prospectively, include the time to diagnosis in their analyses, and screen the region of interest in all study participants with a similar modality scored independently by two trained observers, in an attempt to rule out residual bias. As indicated previously, heritability of aneurysms is estimated to be high, but the largest genome wide association study to date includes only 4 972 patients with AAA.[5] Indication of other aneurysm prone genetic profiles may improve indication of patients at high risk, in addition to established clinical features. In this manner, detailed patient related risk features for specific subtypes of arterial aneurysm co-prevalence can be identified.

Conclusions

Approximately one in six patients with a primary aortic aneurysm and one in four patients with a popliteal artery aneurysm harbours a concurrent aneurysm. Higher age, hypertension, stenotic disease, presence of multiple (at least three) aneurysms, and primary aneurysm size seem predictive of aneurysm co-prevalence. These clinical predictors may assist when deciding whether a patient with a primary aneurysm needs to be screened for additional aneurysms.

CONFLICTS OF INTEREST

None.

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APPENDIX A. SUPPLEMENTARY DATA

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