

Associations of Comorbidities, Medications, Biomarkers, and Hemodynamic Factors with Abdominal Aortic Aneurysm Outcomes: An Umbrella Meta-Analysis

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Abstract

Abdominal aortic aneurysm (AAA) is a life-threatening condition. Although the traditional risk factors for AAA have been identified, the evidence for other influencing factors (comorbidities, drugs, biomarkers, and biomechanical parameters) remains fragmented and lacks comprehensive stratified assessment. This umbrella review synthesized evidence from 36 meta-analyses on risk/protective factors for abdominal aortic aneurysm (presence, growth, and rupture). Conducted per PRISMA 2020 guidelines, it appraised methodological quality (AMSTAR-2) and evidence certainty (GRADE). Analysis of 39 factors identified several supported by moderate-quality evidence. Diabetes was a consistent protective factor against prevalence, growth, and rupture. Similarly, statins use slowed growth and reduced rupture risk, while metformin use reduced AAA growth. For risk factors, hypertension increased incidence, and the biomarkers D-dimer, fibrinogen, and hsCRP were positively associated with AAA presence. Associations for other factors, including various comorbidities, medications, and biomechanical parameters like peak wall rupture index, were less consistent or based on low/very low-quality evidence. This study confirms AAA's multifactorial nature and establishes a clear evidence hierarchy, highlighting diabetes, statins, and metformin as key protective factors. It underscores that most factors lack high-quality evidence, necessitating standardized measurement and prospective studies to improve risk prediction and therapeutic strategies.

Keywords: Abdominal aortic aneurysm; AAA presence; AAA rupture; AAA growth; Lifestyle; Circulating biomarker; Comorbidities; Medication; Biomechanical parameters

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Introduction

Abdominal aortic aneurysm (AAA) is a life-threatening condition characterized by the permanent dilation of the abdominal aorta^[1]. It often remains asymptomatic until rupture, which is associated with very high mortality, in part because many patients die before reaching hospital^[2,3]. Rupture of AAA represents a significant clinical event, having a mortality rate of 90% especially on male groups^[4]. Therefore, the prevention and treatment of AAA are very crucial to reduce many mortality rates. Clinical management is largely guided by aneurysm diameter, with elective repair generally considered once aneurysm size reaches guideline-recommended thresholds (commonly > 5.5 cm in men and > 5.0 cm in women), or earlier in the presence of symptoms or rapid expansion^[5]. However, there is still a lack of key and efficient diagnostic methods in the assessment of AAA. Therefore, exploring the related factors of AAA can reduce its incidence by identifying high-risk populations and promoting early intervention targeting modifiable risk factors.

Given the high mortality^[6] and the often-silent progression of AAA, identifying the factors that contribute to its formation, expansion, and rupture is critical. While traditional risk factors like smoking and age have been well established, other elements—including specific comorbidities, medications, biomarkers, and biomechanical forces—also play a role in AAA pathogenesis^[3,7]. These factors are often studied in isolation, resulting in a fragmented understanding of how they collectively contribute to AAA progression. Despite numerous meta-analyses summarizing evidence on these individual risk factors, the lack of a unified assessment means that a comprehensive, hierarchical assessment of the entire evidence landscape unaddressed.

An umbrella meta-analysis which synthesizes findings from multiple meta-analysis, is uniquely positioned to fill this gap^[8]. By evaluating the strength, consistency, and quality of evidence across various risk and protective factors, this approach offers a hierarchical and integrated perspective on the factors influencing AAA outcomes. This type of analysis not only consolidates fragmented evidence but also helps to identify the most robust associations, ultimately providing more reliable

insights to inform clinical decision-making and guide resource allocation in future research.

This umbrella meta-analysis aims to consolidate findings from published meta-analyses to provide a comprehensive overview and an evaluation of the strength of evidence for risk and protective factors associated with AAA outcomes. By synthesizing and critically appraising existing evidence, we seek to inform clinical practice, guide future research priorities, and contribute to the development of more effective prevention and management strategies for AAA. To our knowledge, this is the first umbrella meta-analysis to integrate evidence across all major domains of AAA risk and protective factors, aiming to provide a definitive hierarchy of evidence to guide clinical priority and future research direction.

Methods

Protocol and registration

This umbrella review was conducted following a predefined protocol, which detailed the research question, eligibility criteria, and methodological approach. The protocol was registered on PROSPERO (Registration No. 1180184). The review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines and established standards for umbrella reviews^[9].

Eligibility criteria

We included systematic reviews and meta-analyses that examined associations between predefined exposures and specific AAA-related outcomes. Eligible studies were screened and downloaded from PubMed, Embase; articles were conducted through September 2025. Key search terms are as follows: (“Abdominal Aortic Aneurysms” OR “Aneurysms, Abdominal Aortic” OR “Aortic Aneurysms, Abdominal” OR “Abdominal Aortic Aneurysm” OR “Aneurysm, Abdominal Aortic”) AND (“Meta-Analysis” OR “Systematic Review”) AND (“Factor, Risk” OR “Factors, Risk” OR “Risk Factor”). Exclusion criteria are included: (1) duplicate publications; (2) non-meta-analyses; (3) studies in which outcomes were not related to AAA prevalence, growth/

progression, or rupture; and (4) studies focused on the prognosis after aortic aneurysm surgery. In brief, eligible exposures were categorized into lifestyles, comorbidities, medications, circulating biomarkers, and biomechanical parameters. Outcomes of interest included AAA presence (including prevalence/incidence), growth rate, and rupture.

Study selection and quality assessment

The study selection process followed the PRISMA flow diagram (Figure 1). Two reviewers independently screened titles, abstracts, and full-text articles. The methodological quality of each included review was appraised using the AMSTAR-2 tool^[10]. In addition, the GRADE system was utilized to assess the quality of evidence for each outcome, classifying it into “high”, “moderate”, “low”, or “very low”^[11]. Any discrepancies during selection or quality assessment were resolved through consensus or by consulting a third reviewer.

Data extraction and synthesis

Data were extracted in duplicate using a standardized form, capturing details on study characteristics, exposures, outcomes, effect estimates, and measures of heterogeneity. Evidence was synthesized separately for each outcome category. Where available, results from subgroup or sensitivity analyses reported in the original reviews were narratively summarized to explore heterogeneity.

Results

Study selection and characteristics

A total of 2081 records were identified through PubMed ($n = 795$) and Embase ($n = 1286$). Following the removal of duplicates and exclusion of irrelevant records, 103 articles were assessed in full text, and 36 non-overlapping systematic reviews or meta-analyses were included. These contributed 49 exposure–outcome associations across 39 distinct risk or protective factors (Figure 1). The included studies evaluated lifestyle factors, comorbidities, circulating biomarkers, medication exposures, and biomechanical parameters related

to AAA presence, growth, or rupture. Related factors are included in the following table (Table 1).

Lifestyle factors

Across lifestyle exposures, 3 analyses were included. Regarding lifestyle, alcohol consumption showed no significant association with AAA (RR 0.93, 95% CI 0.78–1.11; AMSTAR-2: moderate), whereas higher levels of physical activity were associated with reduced AAA presence (RR 0.70, 95% CI 0.56–0.87)^[12,13]. In contrast, obesity demonstrated a positive association with AAA (RR 1.29, 95% CI 1.14–1.46) (Figure 2)^[14].

Comorbidities

Comorbidities contributed a larger evidence base. As shown in Table 2, hypertension was positively associated with AAA presence (RR 1.66, 95% CI 1.49–1.85, $I^2 = 79.3\%$); the underlying meta-analysis reported that heterogeneity was largely driven by a small number of influential studies, with attenuation of I^2 after exclusions while the direction of effect remained stable. Conversely, diabetes consistently^[15–17] associated with more favorable AAA outcomes, including slower aneurysm growth (MD -0.25 mm/year, 95% CI -0.35 to -0.15 ; $I^2 = 73\%$) and lower AAA presence (OR 0.57, 95% CI 0.51–0.63, $I^2 = 89\%$) and was also associated with a lower risk of AAA rupture (OR 0.71, 95% CI 0.56–0.89). Notably, heterogeneity was substantial for both presence and growth, likely reflecting differences in study design, outcome ascertainment, and covariate adjustment. The inverse association was more consistent in prospective studies using adjusted estimates (with substantially reduced heterogeneity), whereas case–control studies showed no significant association. For other cardiovascular comorbidities, COPD was positively associated with AAA presence (OR 1.78, 95% CI 1.38–2.30; $I^2 = 93\%$) but showed no clear association with AAA growth (SMD 0.04, 95% CI -0.07 to 0.15)^[18,19]. Similarly, CAD was associated with higher AAA presence (OR 2.42, 95% CI 2.08–2.81) while its association with AAA growth was small and inconsistent (SMD -0.06 , 95% CI -0.13 to -0.01)^[20,21]. Beyond cardiovascular conditions, simple renal cysts (OR 3.02, 95% CI 2.01–4.56) and primary abdominal wall hernia (OR 2.32, 95% CI 1.72–3.14) were positively associated

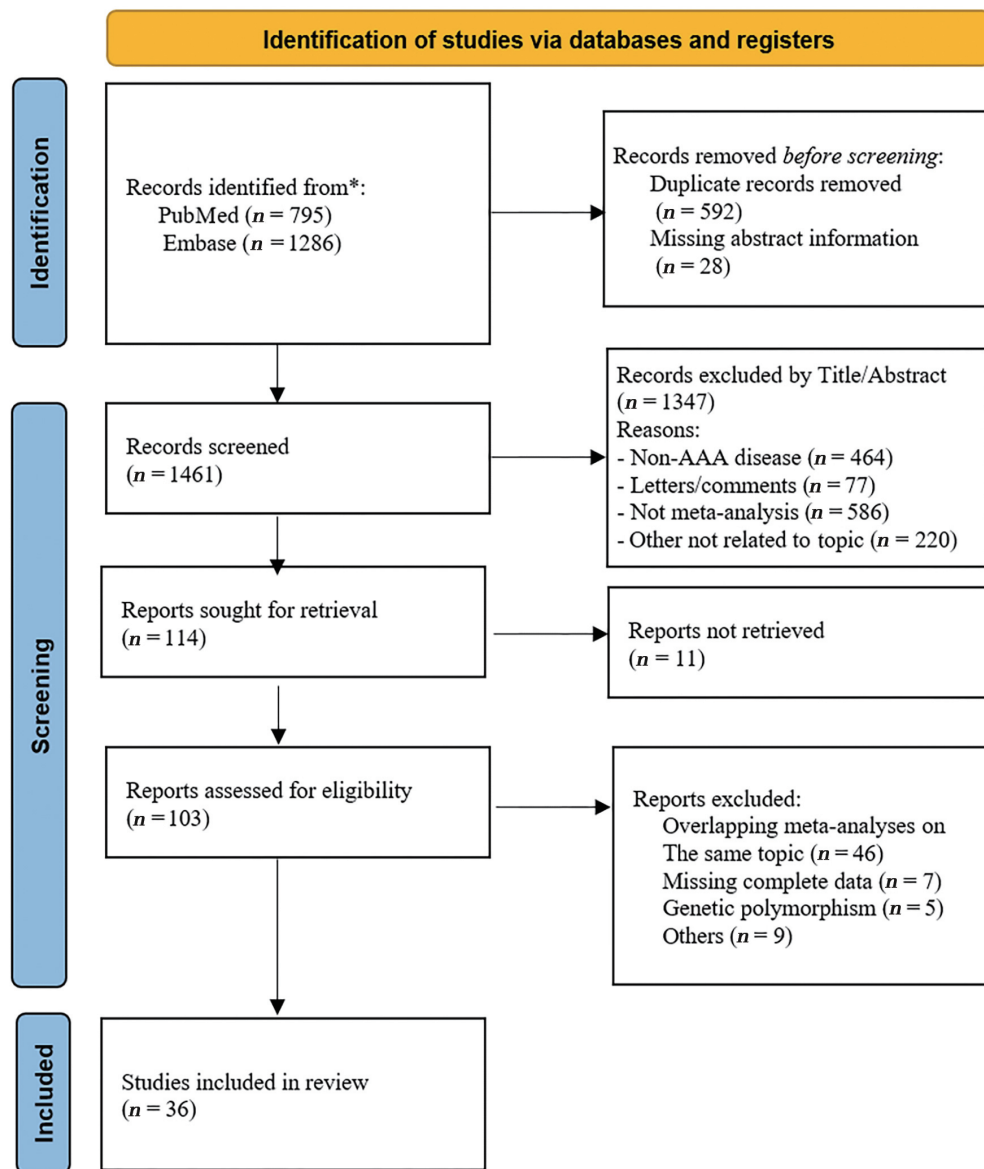


Figure 1: Flow-chart of study selection.

Table 1: AAA related factors

Lifestyle	Alcohol, physical activities, obesity
Comorbidities	Diabetes hypertension, renal cysts, primary abdominal wall hernia, PAD, COPD, CAD, helicobacter pylori infection.
Circulating biomarkers	Lipoprotein A, LDL, HDL, tPA, homocysteine, MMP-9, hsCRP, IL-6, TNF- α , IL-10, D-dimer, zinc and copper, fibrinogen, TAT, prothrombin, platelet count
Medication exposure	Metformin, statins, ACEI, ARBs, beta-blockers, antibiotics, Doxycycline, antiplatelet, tetracyclines, macrolides
Biomechanical parameters	PWS, PWRI

Abbreviations: PAD: peripheral artery disease; CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; ACEI: angiotensin-converting enzyme inhibitors; ARBs: angiotensin ii receptor blockers; PWS: peak wall stress; PWRI: peak wall rupture index.

Author	Year	Exposure	Outcome	Estimate type	Forestplot	Estimate(95% CI)	T/R/C/P	I ²	AMSTAR-2	Grade
Kavaliunaite E.	2017	Alcohol consumption	AAA presence	RR		0.93 (0.78 to 1.11)	10/0/10/0	47%	Low	Very Low
Aune D.	2020	Physical activity	AAA presence	RR		0.70 (0.56 to 0.87)	9/0/9/0	58%	Low	Very Low
Sheng C.	2023	Obesity	AAA presence	RR		1.29 (1.14 to 1.46)	3/0/2/1	0%	Low	Very Low

Figure 2: Associations between lifestyle factors and abdominal aortic aneurysm (AAA).

OR: odds ratio; RR: risk ratio; MD: mean difference; SMD: standardized mean difference; OR: T/R/C/P: T: total amount of studies; R: randomized controlled trial; C: controlled trial/comparative; P: prevalence study.

Table 2: Associations between comorbidities and abdominal aortic aneurysm (AAA) outcome

Author	Year	Exposure	Outcome	Estimate type	Estimate (95% CI)	T/R/C/P	I ²	AMSTAR-2	Grade
Kobeissi E.	2019	Hypertension	AAA presence (risk)	RR	1.66 (1.49 to 1.85)	13/0/13/0	79.3%	Low	Very Low
Alawattegama L.H.	2024	Diabetes	AAA growth	MD	-0.25 (-0.35 to -0.15)	24/5/15/4	73%	Low	Very Low
Jiang Xiong et al.	2018	Diabetes	AAA presence	OR	0.57 (0.51 to 0.63)	7/0/7/0	89%	Very Low	Very Low
Takagi H.	2016	Diabetes	AAA rupture	OR	0.71 (0.56 to 0.89)	11/0/4/7	0%	Low	Very Low
Takagi H.	2016	COPD	AAA growth	SMD	0.04 (-0.07 to 0.15)	9/0/9/0	0%	Low	Low
Takagi H.	2016	COPD	AAA presence	OR	1.78 (1.38–2.30)	11/0/0/11	93%	Low	Low
Takagi H.	2016	CAD	AAA growth	SMD	-0.06 (-0.13 to -0.01)	20/3/17/0	24%	Low	Very Low
Elkalioubie A.	2012	CAD	AAA presence	OR	2.42 (2.08 to 2.81)	9/0/1/8	NR	Low	Very Low
Matthews E.O.	2017	PAD	AAA growth	SMD	-0.13 (-0.27 to 0.00)	15/0/14/1	51%	Moderate	Low
Giannopoulos S.	2021	Renal cysts	AAA presence	OR	3.02 (2.01 to 4.56)	9/0/1/8	88.5%	Low	Very Low
Takagi H.	2015	Primary abdominal wall hernia	AAA presence	OR	2.32 (1.72 to 3.14)	14/0/1/13	82%	Low	Low
Araim M.	2025	Helicobacter pylori infection	AAA presence	RR	1.54 (1.14 to 2.08)	5/0/2/3	81%	Low	Very Low

OR: odds ratio; RR: risk ratio; MD: mean difference; SMD: standardized mean difference; OR: T/R/C/P: T: total amount of studies; R: randomized controlled trial; C: controlled trial/comparative; P: prevalence study.

with AAA presence, although heterogeneity was substantial; sensitivity analyses in the underlying reviews generally supported directionally consistent findings. Finally, *Helicobacter pylori* infection was associated with increased AAA risk (RR 1.54, 95% CI 1.14–2.08) but showed considerable heterogeneity ($I^2 = 81\%$), and the association was attenuated and became non-significant after removal of influential studies, indicating limited robustness^[22–25].

Circulating biomarkers

Eight meta-analyses examined circulating biomarkers spanning coagulation, inflammation, and matrix

remodeling (Figure 3). Across the included meta-analyses, heterogeneity was high for most biomarker associations, with many analyses showing substantial to considerable inconsistency (frequently $I^2 > 75\%$). Only a minority of biomarkers demonstrated moderate heterogeneity. Among coagulation-related markers, D-dimer^[26] was higher in individuals with AAA (MD 325.82, 95% CI 199.74–451.89) and fibrinogen^[26] also showed a positive association (MD 0.43, 95% CI 0.28–0.58). The thrombin–antithrombin (TAT)^[26] complex demonstrated a large mean difference (MD 5.58, 95% CI 3.34–7.83), whereas prothrombin and platelet count were not significantly associated with AAA presence^[26].

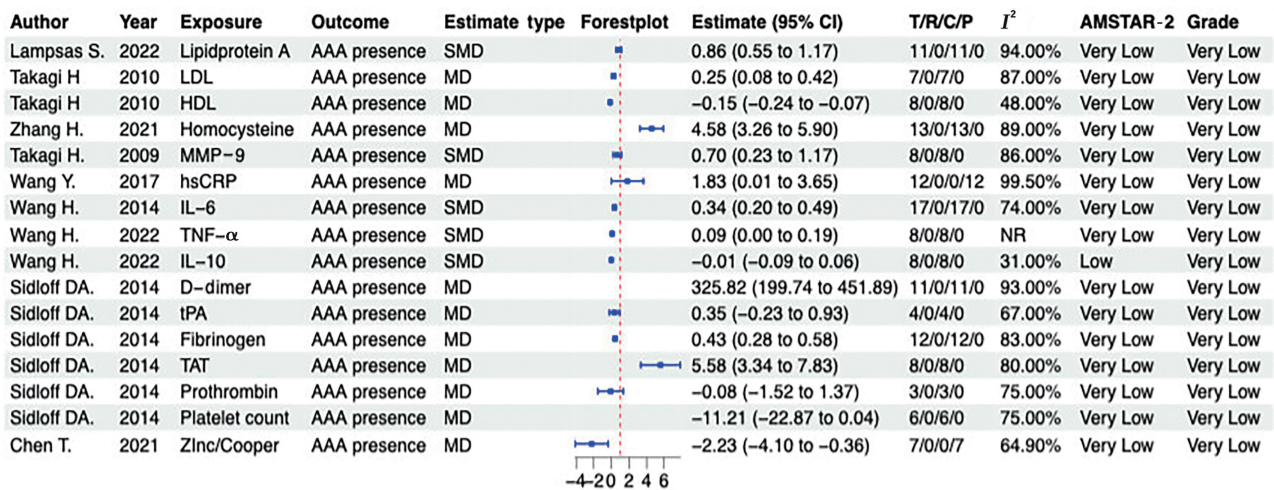


Figure 3: Associations between circulating biomarkers and abdominal aortic aneurysm (AAA) presence.

OR: odds ratio; RR: risk ratio; MD: mean difference; SMD: standardized mean difference; OR: T/R/C/P: T: total amount of studies; R: randomized controlled trial; C: controlled trial/comparative; P: prevalence study.

Regarding inflammatory markers, hsCRP^[27] was higher in AAA cases than controls (MD 1.83, 95% CI 0.01–3.65). IL-6 was positively associated with AAA presence (SMD 0.34, 95% CI 0.20–0.49), while TNF-α showed a small positive association (SMD 0.09, 95% CI 0.00–0.19). In contrast, IL-10 was not associated with AAA presence (SMD -0.01, 95% CI -0.09–0.06)^[28,29].

Regarding extracellular matrix remodeling, MMP-9 was higher in AAA (SMD 0.70, 95% CI 0.23–1.17; $I^2 = 86\%$)^[30]. For lipid-related indicators, HDL^[31] (MD -0.15, 95% CI -0.24 to -0.07) had a protective effect, whereas LDL^[31] (MD 0.25, 95% CI 0.08–0.42) and lipoprotein A^[1] (SMD 0.86, 95% CI 0.55–1.17) were positively associated. Homocysteine^[32] (MD 4.58, 95% CI 3.26–5.9) was also higher in AAA cases. Finally, zinc and copper^[33] were inversely associated with AAA presence (MD -2.23, 95% CI -4.1 to -0.36).

Medication exposures

According to Figure 4, a set of meta-analyses evaluated pharmacologic agents in relation to AAA outcomes. Among these, statins^[34–36] and metformin^[37,38] consistently demonstrated protective associations supported by moderate-quality evidence. Statins showed outcome-specific findings: no significant association with AAA presence (RR 1.83, 95% CI 0.56–5.98), but a protective association with AAA rupture (OR 0.63,

95% CI 0.51–0.78) and reduced AAA growth (MD -1.50, 95% CI -1.99 to -1.02); Metformin was associated with slower AAA growth (MD -0.80, 95% CI -1.12 to -0.47)^[37], yet the evidence was graded as very low quality.

Statins were associated with decreased AAA growth^[34] (SMD 1.50, 95% CI -1.99 to -1.02) and reduced rupture risk^[36] (OR 0.63, 95% CI 0.51–0.78). Metformin similarly reduced AAA presence^[37] (OR 0.61, 95% CI 0.41–0.92) and slowed aneurysm expansion^[38] (OR 0.63, 95% CI 0.51–0.78), representing one of the most consistent findings across medication classes.

Among antihypertensive agents, ACE inhibitors^[39,40] were associated with a modest reduction in rupture risk (OR 0.87, 95% CI 0.81–0.93), but showed no significant association with AAA growth (SMD 0.01, 95% CI -0.26 to 0.28). In contrast, evidence for ARBs^[39] was largely null and highly heterogeneous, with no significant association for rupture (OR 1.24, 95% CI 0.41–3.77; $I^2 = 95.5\%$) or growth (SMD 0.34, 95% CI -0.77 to 1.44; $I^2 = 100\%$). For other medication classes, Beta-blockers^[41] showed no significant association across outcomes (SMD -0.22, 95% CI -0.44 to 0.00), and antiplatelet agents^[42] did not demonstrate significant relationships with AAA progression or rupture (MD -0.04, 95% CI -0.37 to 0.30). Antibiotic-related analyses also showed no significant effects:

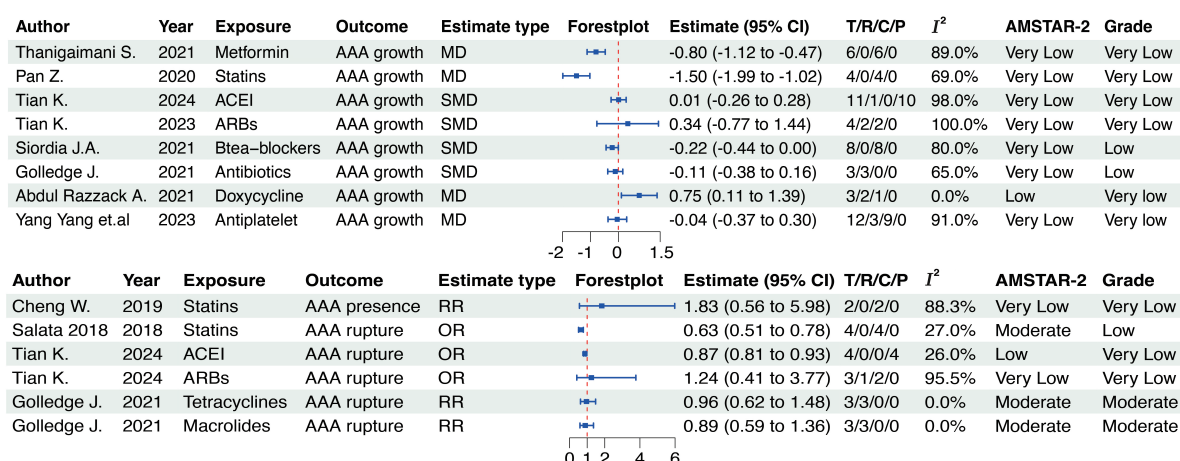


Figure 4: Associations between medication exposures and abdominal aortic aneurysm presence, growth and rupture.

OR: odds ratio; RR: risk ratio; MD: mean difference; SMD: standardized mean difference; OR: T/R/C/P: T: total amount of studies; R: randomized controlled trial; C: controlled trial/comparative; P: prevalence study.

overall antibiotics were not associated with AAA growth (SMD -0.11 , 95% CI -0.38 to 0.16), and neither tetracyclines (RR 0.96 , 95% CI 0.62 – 1.48) nor macrolides (RR 0.89 , 95% CI 0.59 – 1.36) were associated with AAA rupture. Importantly, doxycycline did not demonstrate a protective relationship; instead, it was associated with a small increase in AAA growth (MD 0.75 , 95% CI 0.11 – 1.39), with low certainty ratings^[43,44].

Biomechanical parameters

One meta-analysis evaluated biomechanical stress parameters derived from imaging or computational modeling. Peak wall stress (PWS)^[45] was significantly associated with rupture risk (SMD 0.13 , 95% CI -0.18 – 0.44), while peak wall rupture index (PWRI) also demonstrated a significant positive association (SMD 0.42 , 95% CI 0.14 – 0.70). Both analyses were rated low or very Low in methodological quality (Figure 5).

Discussion

This umbrella review synthesized evidence from 36 systematic reviews and meta-analyses examining lifestyle factors, comorbidities, circulating biomarkers, medications, and biomechanical parameters in relation to AAA outcomes. While effect estimates varied considerably across domains, several exposures demonstrated consistent patterns supported by moderate-quality evidence, whereas others showed null or highly heterogeneous findings. The following discussion integrates these results with existing biological knowledge while acknowledging the limitations inherent to observational evidence.

Lifestyle and comorbidity patterns in AAA

Lifestyle exposures demonstrated heterogeneous associations. Physical activity was inversely associated with AAA presence, whereas obesity showed a

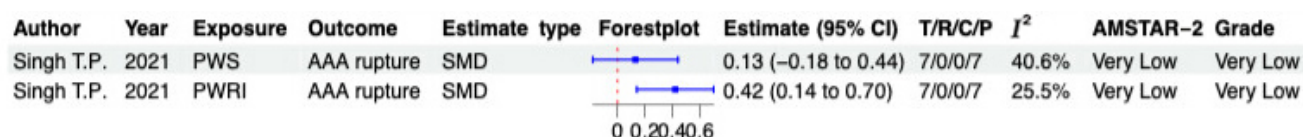


Figure 5: Associations between biomechanical parameters and abdominal aortic aneurysm (AAA) rupture.

OR: odds ratio; RR: risk ratio; MD: mean difference; SMD: standardized mean difference; OR: T/R/C/P: T: total amount of studies; R: randomized controlled trial; C: controlled trial/comparative; P: prevalence study.

positive association^[13,14]. Although causality cannot be inferred from the included evidence, these patterns are biologically plausible given prior literature showing that regular physical activity is associated with lower systemic inflammation and improved metabolic homeostasis, whereas obesity is linked to chronic inflammatory activation, oxidative stress, and adverse metabolic profiles^[13]. These pathways have been implicated in early aortic wall degeneration in both experimental and epidemiologic studies, providing a potential mechanistic context for the observed associations. Conversely, alcohol consumption showed no meaningful association with AAA.

Comorbidity-related findings demonstrated clearer trends, although between-study heterogeneity was frequently substantial. Diabetes^[15–17] showed consistent protective associations across AAA incidence^[16], growth^[15], and rupture^[17]. Importantly, heterogeneity was high for both presence and growth outcomes, and the underlying evidence suggested that the inverse association was more consistent in prospective studies using adjusted estimates, with markedly reduced heterogeneity, whereas case-control studies often showed null associations. This pattern supports the possibility that differences in study design, outcome ascertainment (screen-detected vs. clinically diagnosed AAA), and confounder control—particularly for smoking, adiposity, and medication exposure—partly explain the observed inconsistency. Although these associations cannot be interpreted causally, they align with several proposed mechanisms, including altered extracellular matrix turnover, reduced proteolytic activity, and differential exposure to glucose-lowering agents such as metformin.

Hypertension^[46] was positively associated with AAA incidence but not growth, consistent with the concept that elevated pulsatile pressure may contribute to aneurysm initiation but that subsequent expansion is more strongly influenced by inflammation- and proteolysis-related pathways. Other cardiovascular comorbidities showed strong associations with AAA presence but weaker or inconsistent relationships with growth, highlighting outcome-specific mechanisms and methodological challenges. COPD was positively associated with AAA presence with very high

heterogeneity, which is biologically and epidemiologically plausible given COPD's close correlation with cumulative smoking exposure, systemic inflammation, and protease-antiprotease imbalance; however, the null association with growth suggests that COPD may act more as a marker of shared exposures and susceptibility than as a driver of aneurysm expansion^[20,21]. Similarly, CAD was associated with higher AAA presence, consistent with shared atherosclerotic risk profiles and generalized vascular pathology, while its association with growth was small and inconsistent, raising the possibility that any true effect on expansion is modest^[18,19].

Beyond traditional cardiovascular conditions, simple renal cysts and primary abdominal wall hernia were positively associated with AAA presence, albeit with substantial heterogeneity^[23,24]. These associations may point toward shared underlying structural susceptibility—such as altered connective tissue integrity or extracellular matrix remodeling—rather than only conventional risk factors. However, detection and selection biases are plausible: individuals undergoing abdominal imaging for unrelated reasons are more likely to have both incidental cysts and asymptomatic AAA identified. Finally, the association between *Helicobacter pylori* infection and AAA risk appeared less robust, with considerable heterogeneity and attenuation to non-significance after removal of influential studies, suggesting that the observed signal may be context-dependent such as population, assay method, or unmeasured confounding and should be interpreted cautiously.

Biological pathways reflected by circulating biomarkers

Evidence from circulating biomarkers broadly supports a multifactorial biological model of AAA pathogenesis involving coagulation, inflammation, and extracellular matrix remodeling. Lipid-related biomarkers revealed an atherosclerotic pattern: patients with AAA had lower levels of HDL and higher levels of LDL and lipoprotein(a)^[47]. Homocysteine levels were also elevated (MD 4.58). These findings are consistent with the similar risk structure of AAA and atherosclerotic cardiovascular disease, suggesting that

circulating lipid profiles and related metabolic factors may reflect systemic vascular vulnerability, rather than a mechanism specific to AAA.

Coagulation-related markers showed the most prominent differences, with higher D-dimer, fibrinogen, and a large increase in thrombin-antithrombin complex among individuals with AAA. This pattern is consistent with the biological importance of the intraluminal thrombus, which can sustain thrombin generation and fibrin turnover while promoting inflammatory and proteolytic activity. In contrast, platelet count, and prothrombin were not significantly associated, supporting the notion that AAA is more strongly reflected by markers of activation and turnover than by static hematologic indices.

MMP-9 was higher in AAA with considerable heterogeneity^[47]. This association is biologically coherent with elastin and collagen degradation contributing to aortic wall weakening, and MMP-9 has been repeatedly implicated in AAA tissue remodeling. Inflammatory biomarkers showed broadly positive but generally modest associations with AAA presence. Systemic inflammation may represent a favorable environment for coexistence with AAA and is associated with known risk factors such as smoking and systemic atherosclerosis, rather than being specific to AAA. Secondly, key inflammatory processes in AAA may be highly confined to the aortic wall and intraluminal thrombus (ILT) microenvironment; therefore, peripheral measurements may dilute biologically significant local gradients. Furthermore, cytokine detection is highly sensitive to pre-analytical factors (sample processing, time, storage), which can exacerbate inter-study inconsistencies. The lack of correlation for IL-10 may reflect a true absence of systemic anti-inflammatory signatures or limitations in measurement and confounding factors; this also suggests that not all immune pathways involved in AAA tissue studies translate into detectable circulating differences. The evidence base remains limited by variability in assay methods, inconsistent adjustment for confounders, and the cross-sectional nature of most studies^[26,27,30].

Medication exposures and potential therapeutic modifiers

Among medication exposures, statins and metformin^[37,38] demonstrated the most consistent protective associations with AAA outcomes^[34–36]. These findings do not imply causality but are compatible with known pharmacologic properties of these drugs, including anti-inflammatory effects, modulation of oxidative stress pathways, inhibition of matrix metalloproteinases, and improvements in endothelial function. These mechanistic pathways provide biological plausibility for the observed associations and justify further investigation in prospective cohorts and randomized controlled trials. ACE inhibitors^[39,40] showed a modest association with reduced rupture risk, but evidence for other antihypertensive classes—including ARBs^[39] and beta-blockers^[41]—was inconsistent or null. These findings suggest that not all cardiovascular medications exert meaningful influence on aneurysmal processes, and many may act on pathways peripheral to AAA biology. Similarly, antibiotic^[44] therapies showed no convincing benefit, paralleling the broader decline of infectious or inflammatory hypotheses in explaining AAA etiology. Collectively, medication-related results highlight the need for targeted pharmacologic trials that specifically address AAA-related biological pathways rather than extrapolating from cardiovascular disease management more broadly.

Structural determinants: insights from biomechanical parameters

Biomechanical findings were limited but offered important signals. Peak wall rupture index (PWRI)^[45], which incorporates wall stress and thickness, was positively associated with rupture risk, whereas peak wall stress alone was not. These findings align with biomechanical theory suggesting that rupture reflects the interaction between local stress and local strength. However, substantial variability in imaging modalities, segmentation thresholds, and computational modeling parameters limits the comparability of existing studies. Prospective, standardized biomechanical analyses are needed before incorporating these metrics into routine risk stratification.

Evidence map insights and key research gaps

The evidence landscape synthesized in this umbrella review demonstrates substantial variation in certainty across exposure categories. While relatively consistent findings were observed for statins, metformin, diabetes, hypertension, and several circulating biomarkers, most other domains were characterized by sparse data, low methodological quality, or inconsistent results. Notably, most of the available evidence focused on AAA presence rather than clinically decisive outcomes such as aneurysm growth or rupture, which remain underrepresented and heterogeneously measured. High between-study variability—stemming from differences in study design, exposure definitions, biomarker assays, and imaging or computational methods—further limits interpretability. Moreover, the predominance of observational evidence restricts causal inference, and limited mechanistic integration across studies prevents the development of comprehensive, multiparametric risk models.

Based on this evidence map, we offer conservative, evidence-graded implications for clinicians and researchers. What can be implemented now: statin therapy should be guided by established cardiovascular prevention indications in patients with AAA^[48], given its proven cardiovascular benefit and the recurrent associations observed across reviews, while recognizing that this does not constitute definitive AAA-specific causal evidence. What requires further research before routine use: diabetes-related pathways and metformin exposure show relatively consistent inverse associations with AAA outcomes^[49], but metformin use in non-diabetic individuals should remain investigational until adequately powered, mechanistically grounded randomized trials or high-quality prospective cohorts confirm benefit, define target populations, and clarify safety. Several circulating biomarkers also demonstrated recurring associations; however, routine biomarker-guided surveillance is premature because feasibility is constrained by assay cost and availability, and translation requires standardized pre-analytical handling, platform harmonization, calibration, and clinically validated thresholds across laboratories^[3]. What is not recommended for AAA-specific management: antibiotics or infection-targeted strategies

should not be used to modify AAA risk outside clinical trials, given limited robustness, and inconsistent findings across reviews.

Limitations

This umbrella review has several limitations that should be considered when interpreting its findings. First, the evidence base primarily comprises observational studies summarized within existing meta-analyses; therefore, most associations are susceptible to residual confounding and cannot establish causality. As an umbrella review, our conclusions depend on the quality and analytical choices of the included meta-analyses, and inconsistent effect metrics and outcome definitions, together with frequent between-study heterogeneity and sparse evidence for several domains, limited our ability to standardize and synthesize effects across studies. Second, as an umbrella review, our findings are dependent on the methodological quality and analytic decisions of the included meta-analyses; many reviews were rated low/very low by AMSTAR-2 due to inadequate reporting, lack of protocol registration, and incomplete risk-of-bias assessment, and publication bias cannot be excluded—particularly for medication and biomarker domains where null results may be underreported. Third, residual confounding and publication bias represent key limitations of the underlying observational evidence. Unmeasured or incompletely controlled factors—particularly smoking intensity, concomitant cardiovascular medications, healthcare utilization/surveillance, and competing risks—may partly or fully explain several observed associations, including the apparent inverse association of diabetes with AAA outcomes. In addition, publication bias cannot be excluded, especially in medication and biomarker domains where small positive studies may be preferentially published and subsequently meta-analyzed while null findings are underreported, potentially inflating pooled effects even when formal assessments are underpowered or inconsistently reported. Finally, because this review relied on previously published meta-analyses, it was not possible to reanalyze primary data, harmonize covariate adjustments, or explore subgroup-specific associations beyond what was reported.

Conclusion

This umbrella review summarizes current evidence on lifestyle factors, comorbidities, biomarkers, medications, and biomechanical parameters associated with abdominal aortic aneurysm. Statins metformin, diabetes, and several biomarkers—including D-dimer, fibrinogen, and hsCRP—emerged as the most consistently associated exposures, whereas many other factors showed limited or heterogeneous evidence. These findings highlight the multifactorial nature of AAA and emphasize the need for standardized biomarker and imaging approaches, mechanistically informed trials, and integrated risk prediction models to improve surveillance and identify effective therapeutic strategies.

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Conflicts of interest

The authors declare no conflict of interest.

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Registration information

The protocol was registered on PROSPERO (Registration No. 1180184).

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