Aortic Aneurysm and Genetics: Systematic Review with ☸SAIMSARA.

Abstract: This paper aims to systematically review and synthesize the current understanding of genetic factors associated with aortic aneurysms, including specific gene variants, polygenic risk, hereditary syndromes, and the interplay between genetics and environmental factors, to identify key research trends and future directions. The review utilises 223 studies with 1133940 total participants (naïve ΣN). Genetic factors are consistently associated with an increased risk of aortic aneurysms, with observed risk multipliers ranging from 1.08 to 13.5, and a median increased risk of 1.75 across various genetic markers and polygenic risk scores. This genetic influence is evident across different aneurysm types, affecting both syndromic and sporadic cases, and interacts with environmental and clinical risk factors. The generalizability of these findings is somewhat limited by the heterogeneity of study designs and populations. The most significant limitation affecting certainty is the Study Design Heterogeneity, which complicates the synthesis of a unified understanding of genetic contributions. A crucial next step for clinicians is to consider family history and genetic testing, particularly for heritable thoracic aortic diseases, to facilitate early diagnosis and personalized management.

Keywords: Aortic Aneurysm; Genetics; Genetic Variants; Abdominal Aortic Aneurysm; Thoracic Aortic Aneurysm; Polygenic Risk Score; Genome-Wide Association Study; Hereditary Aortopathy; Bicuspid Aortic Valve; Molecular Genetics

Review Stats

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- Source: Semantic Scholar
- Scope: All fields
- Keyword Gate: Fuzzy (≥60% of required terms, minimum 2 terms matched in title/abstract)
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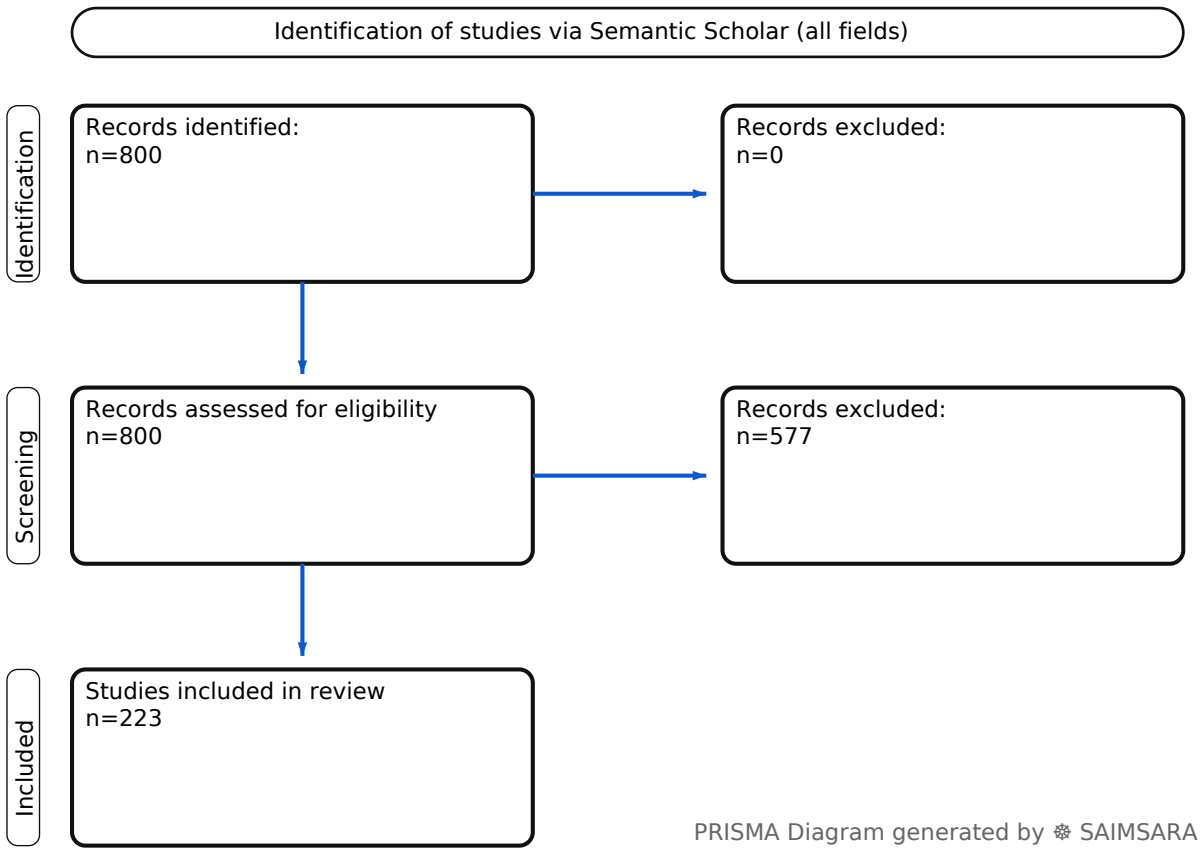
- Included original Abstracts/Papers: 223
- Total study participants (naïve ΣN): 1133940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Screening
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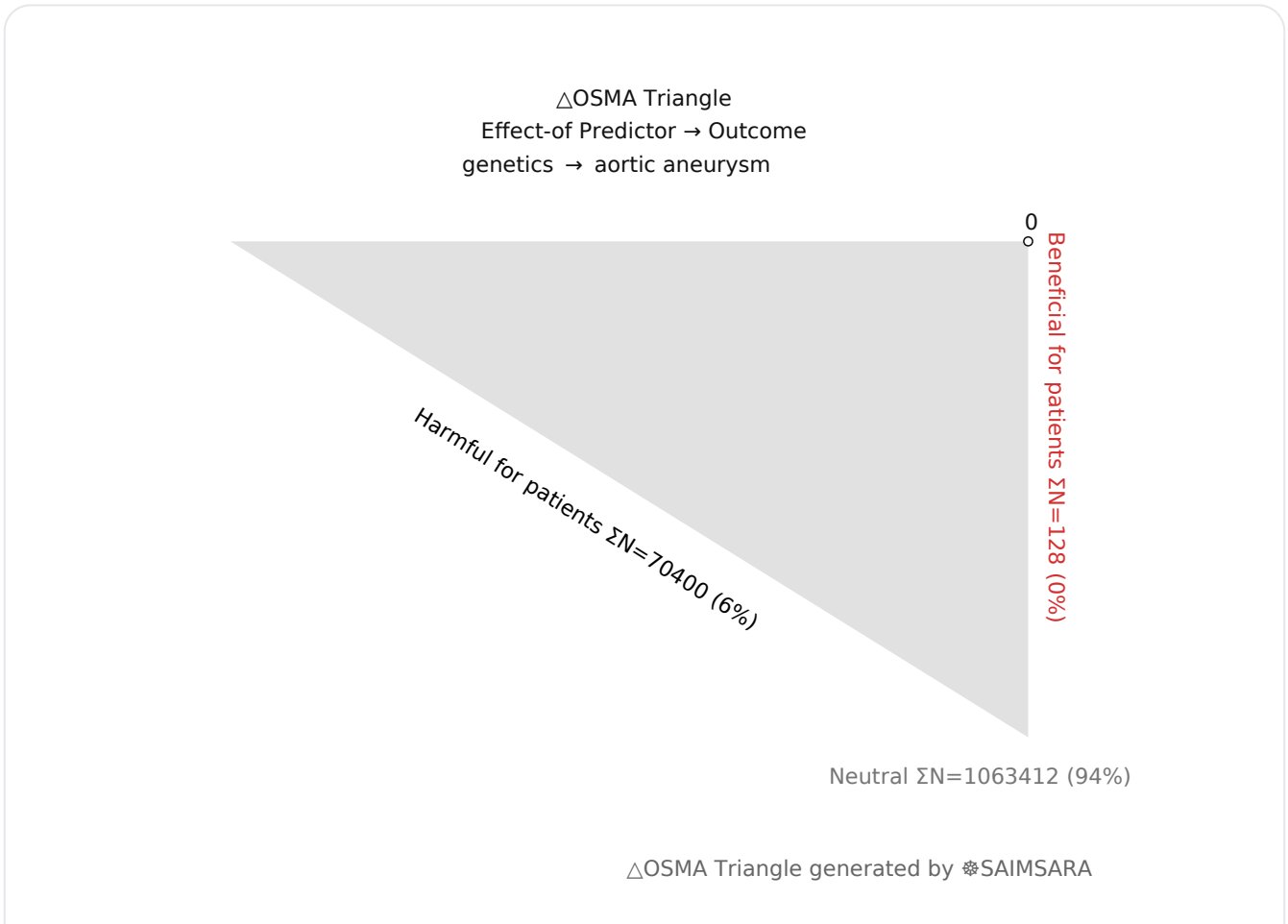
PRISMA Diagram generated by ☸ SAIMSARA


△OSMA Triangle
Effect-of Predictor → Outcome
genetics → aortic aneurysm
0
Beneficial for patients ΣN=128 (0%)
Harmful for patients ΣN=70400 (6%)
Neutral ΣN=1063412 (94%)
△OSMA Triangle generated by ☸SAIMSARA

Outcome-Sentiment Meta-Analysis (OSMA): *(LLM-only)*

Frame: Effect-of Predictor → Outcome • *Source*: Semantic Scholar

Outcome: aortic aneurysm Typical timepoints: peri/post-op, 65-y. Reported metrics: %, CI, p.

Common endpoints: Common endpoints: mortality, complications, survival.

Predictor: genetics — exposure/predictor. Doses/units seen: 100 ml. Routes seen: oral. Typical comparator: those without hs, clinical risk factors alone, control subjects, control….

- **1) Beneficial for patients** — aortic aneurysm with genetics — [49] — ΣN=128
- **2) Harmful for patients** — aortic aneurysm with genetics — [26], [32], [42], [45], [52], [53], [71], [73], [75], [92], [96], [138], [148], [176] — ΣN=70400
- **3) No clear effect** — aortic aneurysm with genetics — [1], [2], [3], [4], [5], [6], [7], [8], [9], [10], [11], [12], [13], [14], [15], [16], [17], [18], [19], [20], [21], [22], [23], [24], [25], [27], [28], [29], [30], [31], [33], [34], [35], [36], [37], [38], [39], [40], [41], [43], [44], [46], [47], [48], [50], [51], [54], [55], [56], [57], [58], [59], [60], [61], [62], [63], [64], [65], [66], [67], [68], [69], [70], [72], [74], [76], [77], [78], [79], [80], [81], [82], [83], [84], [85], [86], [87], [88], [89], [90], [91], [93], [94], [95], [97], [98], [99], [100], [101], [102], [103], [104], [105], [106], [107], [108], [109], [110], [111], [112], [113], [114], [115], [116], [117], [118], [119], [120], [121], [122], [123], [124], [125], [126], [127], [128], [129], [130], [131], [132], [133], [134], [135], [136], [137], [139], [140], [141], [142], [143], [144], [145], [146], [147], [149], [150], [151], [152], [153], [154], [155], [156], [157], [158], [159], [160], [161], [162], [163], [164], [165], [166], [167], [168], [169], [170], [171], [172], [173], [174], [175], [177], [178], [179], [180], [181], [182], [183], [184], [185], [186], [187], [188], [189], [190], [191], [192], [193], [194], [195], [196], [197], [198], [199], [200], [201], [202], [203], [204], [205], [206], [207], [208], [209], [210], [211], [212], [213], [214], [215], [216], [217], [218], [219], [220], [221], [222], [223] — ΣN=1063412

1) Introduction

Aortic aneurysms (AA), encompassing abdominal aortic aneurysms (AAA) and thoracic aortic aneurysms (TAA), represent a significant cardiovascular health burden. These conditions involve localized dilation of the aorta, increasing the risk of rupture and dissection, which are often fatal events [105, 162]. While traditional risk factors such as age, smoking, and hypertension are well-established, a substantial body of evidence increasingly points to a complex genetic architecture underlying aneurysm susceptibility, initiation, and progression [22, 23, 30, 33, 35, 44, 48, 132, 162, 164]. Genetic factors contribute to both syndromic forms, like Marfan and Loeys-Dietz syndromes,

and nonsyndromic, sporadic cases, influencing various molecular pathways critical for aortic wall integrity [17, 41, 46, 159, 180, 191]. Understanding these genetic predispositions is crucial for improved risk stratification, early diagnosis, and the development of personalized therapeutic strategies.

2) Aim

This paper aims to systematically review and synthesize the current understanding of genetic factors associated with aortic aneurysms, including specific gene variants, polygenic risk, hereditary syndromes, and the interplay between genetics and environmental factors, to identify key research trends and future directions.

3) Methods

Systematic review with multilayer AI research agent: keyword normalization, retrieval & structuring, and paper synthesis (see SAIMSARA About section for details).

- **Bias:** Qualitatively inferred from study design fields. The summary includes a mix of cohort, case-control, and mixed-design studies, with a notable number of review articles and studies where the study type was not specified. Many studies lacked detailed population or sample size information in the provided summary, making a comprehensive assessment of selection or reporting bias challenging. The presence of numerous mixed-design studies suggests potential heterogeneity in methodologies and outcomes.

4) Results

4.1 Study characteristics

The included studies primarily comprised cohort, case-control, and mixed-design investigations, with a significant number of reviews and articles where the study design or directionality was not specified. Populations varied, including patients with AAA, TAA, ascending aortic aneurysm (AscAA), bicuspid aortic valve (BAV), Marfan syndrome, and general population cohorts. Sample sizes ranged from individual case reports [37, 194, 223] to large multi-ethnic cohorts of hundreds of thousands of participants [26, 42, 66, 69, 114, 129, 218, 221]. Follow-up periods, when reported, varied from short-term (e.g., 14 days [95, 129]) to long-term (e.g., 24.3 years [77], 25 years [184], 50 years [91]).

4.2 Main numerical result aligned to the query

Genetic factors are consistently associated with an increased risk of aortic aneurysms, with reported risk multipliers (Odds Ratios, Hazard Ratios, or fold increases) ranging from 1.08 to 13.5. The median increased risk observed across various genetic associations and polygenic risk scores was 1.75 [6, 42, 53, 148, 193, 212]. For instance, pathogenic variants in hereditary thoracic aortic aneurysm and

dissection (HTAAD) genes conferred a 13.5-fold increased risk of thoracic aortic aneurysm and dissection (TAAD) [4], while specific HLA alleles showed an Odds Ratio (OR) of 4.7 for AAA in Mexican Mestizo patients [148]. Polygenic risk scores (PRS) for thoracic aortic aneurysm (TAA) demonstrated an OR of 1.50 per standard deviation increase [42] and a Hazard Ratio (HR) of 1.42 per standard deviation [53]. This highlights significant heterogeneity in the magnitude of genetic risk across different aneurysm types and genetic markers.

4.3 Topic synthesis

- **Specific Gene Variants:** Numerous genes are implicated in aortic aneurysm development, including *CALB2* for AAA risk and progression [1, 2], *FBN1* in Marfan syndrome and AAA [52, 114], *TGFBR2* in Loeys-Dietz syndrome [37], *NOTCH1* in aneurysm formation, especially with bicuspid aortic valve (BAV) [21], *SMAD6* in BAV-associated TAA [94, 102], *MYH11* in TAAD and patent ductus arteriosus [183, 186], and *ROBO4* in bicuspid aortic valve and ascending aortic aneurysm (AscAA) [11]. Other identified variants include *CCDC39*, *ANKS6*, *ACVR2B* for sporadic AscAA [7], *DAB2IP* for AAA susceptibility [32], *ELN* for increased aortic aneurysm risk [218], *PCSK9* as a therapeutic target for AAA [26, 69, 221], and *PCSK6* elevated in AAA/TAA tissues [220, 222].
- **Polygenic Risk Scores (PRS):** Polygenic risk scores are increasingly recognized for explaining AAA risk beyond clinical factors [5], predicting thoracic aortic aneurysm (TAA) risk (OR 1.50 per SD PRS, p=6.30x10-03) and the need for surgical intervention [42], and improving the prediction of thoracic aortic diameter [197]. Common variant risk can also modify rare variant TAAD risk [6].
- **Hereditary Aortic Syndromes:** Syndromic aortopathies, such as Marfan syndrome (caused by *FBN1* variants) [52, 25, 41, 114, 159, 199], Loeys-Dietz syndrome (*TGFBR2* mutations) [37, 41, 182], vascular Ehlers-Danlos syndrome [41], and hereditary thoracic aortic aneurysm and dissection (HTAAD) [4, 6, 17, 41, 46, 180], are well-established. Turner syndrome is also associated with an increased risk of aortic dissection [184], and a compound genetic burden including a *MYLK* variant was noted in Oculo-facio-cardio-dental (OFCD) syndrome [194].
- **Bicuspid Aortic Valve (BAV) Aortopathy:** BAV is a significant risk factor for aortopathy, with a strong genetic basis [15, 28, 29, 39, 50, 110, 116]. Studies indicate distinct molecular mechanisms in BAV-associated aneurysms compared to tricuspid aortic valve (TAV) patients, involving impaired splicing of fibronectin [145], endothelial/epithelial-mesenchymal transition [104], and differential TGF-β signaling [97, 120, 134, 188]. Genetic contribution often exceeds environmental factors in BAV aortopathy [176].
- **Gene-Environment Interactions and Risk Factors:** Genetic predisposition may exacerbate effects of environmental exposures [3]. Genetically predicted lipid levels (e.g.,

LDL-cholesterol, total cholesterol, triglycerides) are positively correlated with AA risk, while HDL-C is negatively correlated [8, 212]. Inflammation is a common denominator [18, 20, 67, 69], with specific genetic variants (e.g., *IL6R* Asp358Ala allele conferring protection from AAA [49]) and biomarkers (e.g., heme oxygenase-1 [70]) playing roles. Diabetes mellitus is inversely associated with AA risk [84], and metformin use may reduce AA risk [117]. Vitamin D receptor polymorphisms interact with vitamin D levels to influence AAA risk [66].

- **Molecular Mechanisms of Pathogenesis:** Key pathways include TGF-β signaling [17, 36, 71, 130], extracellular matrix dysregulation (elastin disarray, collagen, proteoglycan accumulation) [69, 115, 216, 218], vascular smooth muscle cell (VSMC) dysfunction (disrupted contraction, apoptosis) [12, 115, 157], and inflammation [69, 115, 171]. Metabolic reprogramming is highlighted as a driver of AAA progression [86], and a molecular signature of endothelial/epithelial-mesenchymal transition is seen in BAV patients [104].
- **Diagnostic and Prognostic Biomarkers:** Proteome-wide Mendelian randomization identified proteins like *COL6A3* and *PRKD2* associated with AAA risk [9]. Soluble glycoprotein VI (sGPVI) is highly predictive of AAA diagnosis and growth rate [62, 127]. Elevated plasma D-dimer and thrombin-antithrombin (TAT) complex are strong independent predictors of AAA growth [96]. Other potential biomarkers include Calbindin 2 (CALB2) [1, 2], miR-24 and Chi3l1 [123], and trimethylamine N-oxide (TMAO) for AAA incidence and growth [73, 75].
- **Familial Aggregation and Heritability:** Aortic dimensions are heritable [50], and familial cases of AAA and TAA show a significant proportion of relatives with aortic dilation and pathogenic mutations in aneurysm genes [45]. The liability to AAA is highly heritable [181], and family-based care facilitates timely diagnosis and reduces adverse events [114].
- **Genetic Testing and Personalized Management:** Molecular diagnostics are increasingly important for hereditary aortic disease [46]. Genetic testing can inform surgical treatment decisions for TAA [47], and accurate diagnosis of heritable thoracic aortic diseases requires integrating clinical assessment with molecular genetic testing and family screening [113]. Genetic profiling is advocated for personalized management [130].

5) Discussion

5.1 Principal finding

Genetic factors are significantly associated with an increased risk of aortic aneurysms, with observed risk multipliers ranging from 1.08 to 13.5, and a median increased risk of 1.75 across various genetic markers and polygenic risk scores [4, 6, 42, 53, 148, 193, 212].

5.2 Clinical implications

- **Early Diagnosis and Screening:** Genetic testing can identify individuals at high risk, particularly in familial cases or those with syndromic features, enabling earlier screening and intervention [113, 114].
- **Personalized Risk Stratification:** Polygenic risk scores and specific gene variants can refine risk assessment beyond traditional clinical factors, guiding surveillance intensity and timing of intervention [5, 42, 83].
- **Targeted Therapies:** Identification of genes and molecular pathways (e.g., PCSK9, TGF-β signaling, GPVI) suggests potential targets for pharmaceutical interventions to prevent or slow aneurysm progression [26, 62, 69, 71, 117, 221].
- **Family-Based Care:** Genetic counseling and family screening are crucial for identifying at-risk relatives and facilitating timely diagnosis, especially for heritable thoracic aortic diseases [113, 114].
- **Bicuspid Aortic Valve Management:** Recognition of distinct genetic and molecular pathways in BAV-associated aortopathy necessitates specific aneurysm prevention strategies for these patients [136, 176].

5.3 Research implications / key gaps

- **Multi-Omics Integration:** Future studies should integrate genomic, proteomic, and metabolomic data to comprehensively map the molecular landscape of aneurysm pathogenesis and identify novel biomarkers [9, 86, 89, 100, 112].
- **Functional Validation Studies:** Further functional studies are needed to elucidate the precise mechanisms by which identified genetic variants contribute to aortic wall degradation and aneurysm formation, moving beyond association to causality [11, 12, 71, 115].
- **Gene-Environment Interaction Studies:** Research should focus on comprehensively characterizing the interactions between genetic predispositions and environmental factors (e.g., xenobiotics, gut microbiome, vitamin D) to understand their combined impact on aneurysm risk and progression [3, 66, 77, 129].
- **Longitudinal Cohort Validation:** Large, prospective longitudinal cohorts are essential to validate the predictive power of polygenic risk scores and novel biomarkers across diverse populations and to assess their impact on long-term clinical outcomes [42, 53, 83, 197].
- **Therapeutic Development:** Studies are needed to translate genetic and mechanistic insights into novel therapeutic strategies, including drug repurposing and development of targeted interventions based on specific genetic profiles [62, 69, 95, 117, 221].

5.4 Limitations

- **Study Design Heterogeneity** — The included literature comprises a wide array of study designs, from case reports to large cohort studies, limiting direct comparability and meta-analysis.
- **Population Specificity** — Many studies lacked detailed population demographics or were focused on specific ethnic groups, which may limit the generalizability of genetic findings across diverse populations.
- **Limited Functional Validation** — While numerous genetic associations were identified, the extent of functional validation for many variants and their precise pathogenic mechanisms remains underexplored.
- **Incomplete Gene-Environment Data** — The complex interplay between genetic factors and environmental exposures is acknowledged but often not fully quantified or mechanistically explained in the current literature.
- **Varied Outcome Metrics** — Different studies reported risk using various metrics (e.g., fold increase, OR, HR) and for different aneurysm types, making a unified quantitative synthesis challenging.

5.5 Future directions

- **Multi-Omics Integration** — Integrate genomic, proteomic, and metabolomic data to uncover comprehensive molecular pathways.
- **Longitudinal Cohort Studies** — Conduct large, diverse, prospective studies to validate genetic risk models and biomarkers.
- **Functional Genomics Research** — Perform in vitro and in vivo studies to confirm causal roles of identified genetic variants.
- **Personalized Risk Models** — Develop and test integrated risk models combining genetic, clinical, and environmental factors.
- **Genetic Screening Guidelines** — Establish evidence-based guidelines for genetic testing and family screening in various aneurysm contexts.

6) Conclusion

Genetic factors are consistently associated with an increased risk of aortic aneurysms, with observed risk multipliers ranging from 1.08 to 13.5, and a median increased risk of 1.75 across various genetic markers and polygenic risk scores [4, 6, 42, 53, 148, 193, 212]. This genetic influence is evident across different aneurysm types, affecting both syndromic and sporadic cases, and interacts with environmental and clinical risk factors. The generalizability of these findings is somewhat limited by

the heterogeneity of study designs and populations. The most significant limitation affecting certainty is the **Study Design Heterogeneity**, which complicates the synthesis of a unified understanding of genetic contributions. A crucial next step for clinicians is to consider family history and genetic testing, particularly for heritable thoracic aortic diseases, to facilitate early diagnosis and personalized management.

References

SAIMSARA Session Index — session.json

Figure 1. Publication-year distribution of included originals

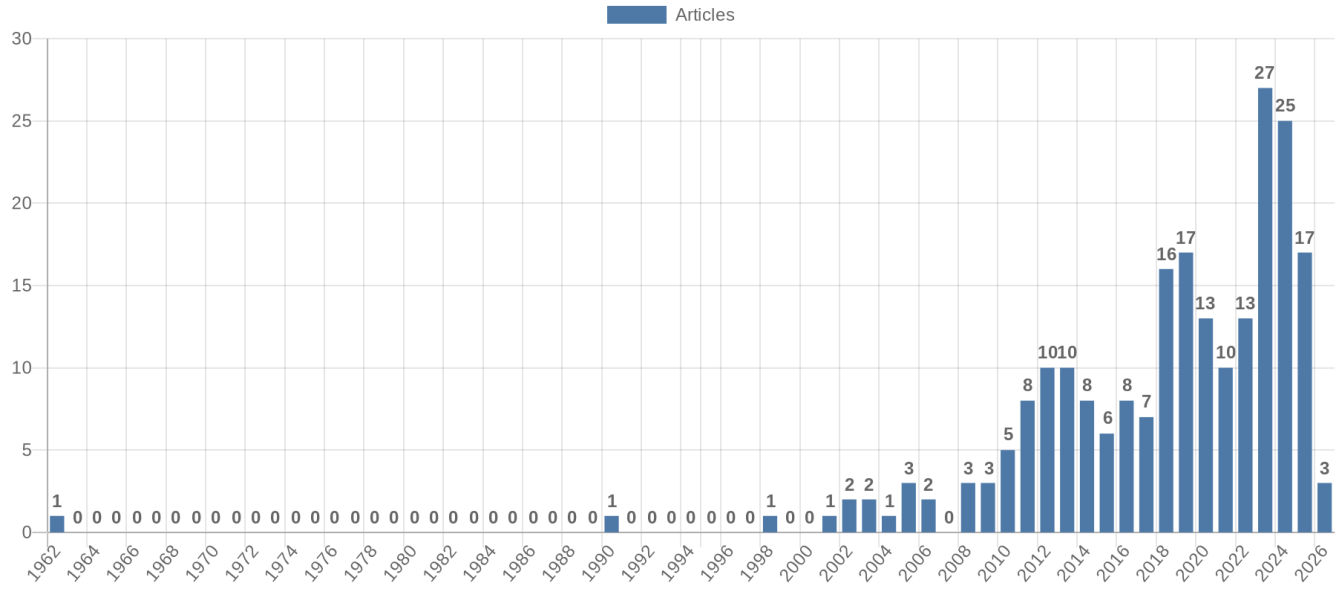


Figure 2. Study-design distribution of included originals

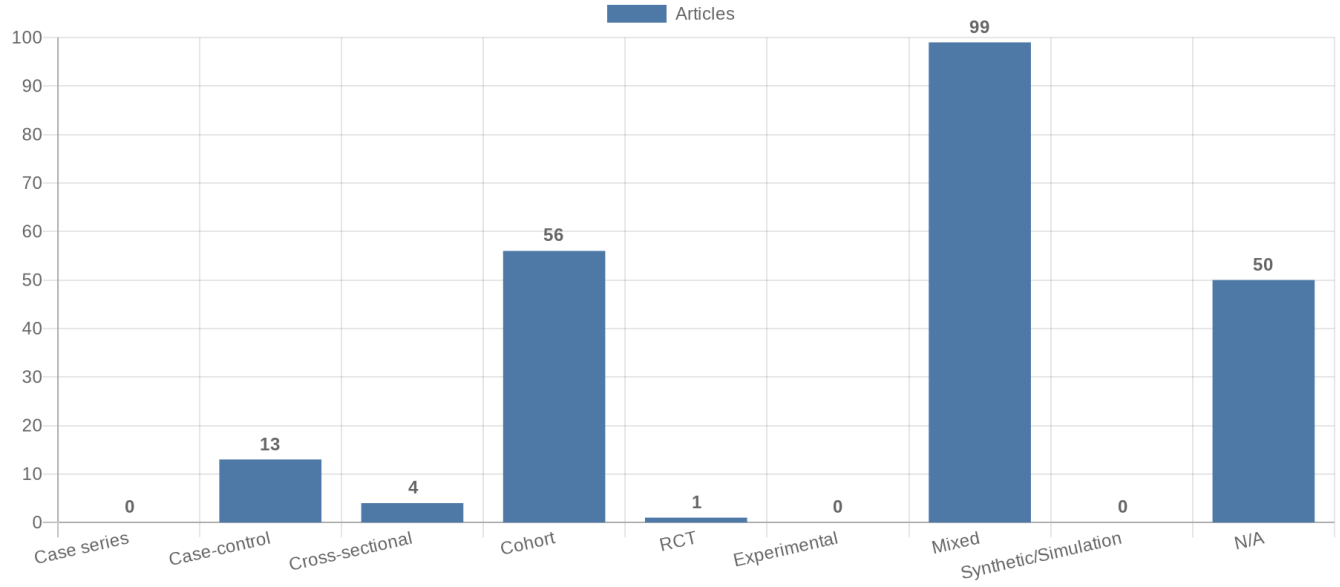


Figure 3. Study-type (directionality) distribution of included originals

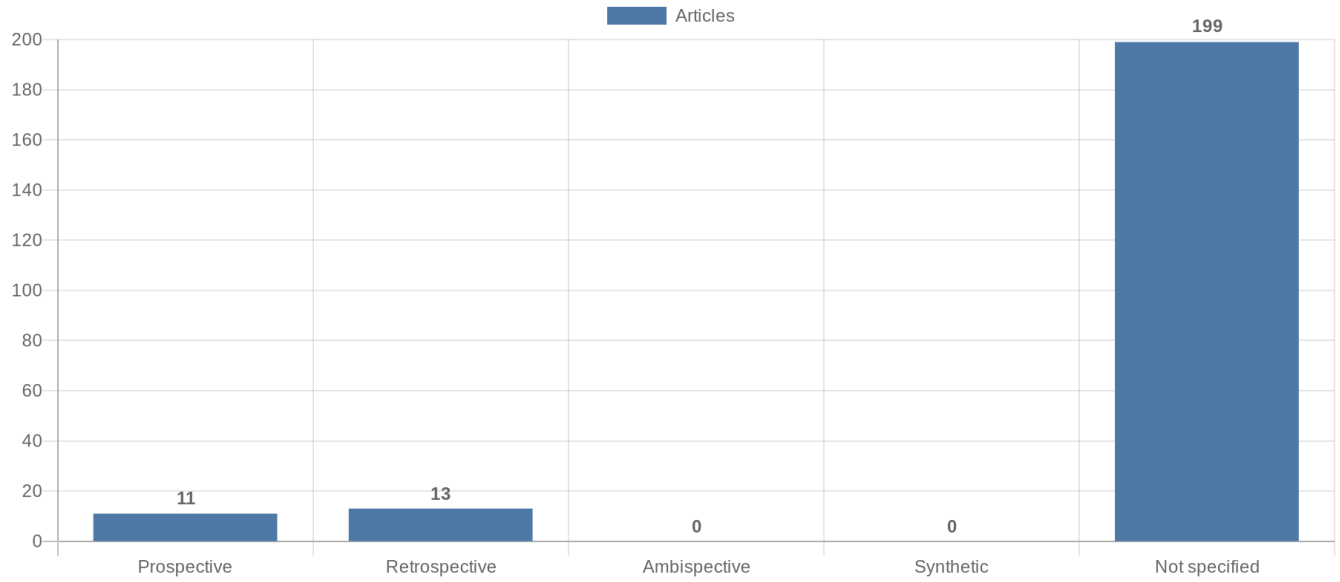


Figure 4. Main extracted research topics

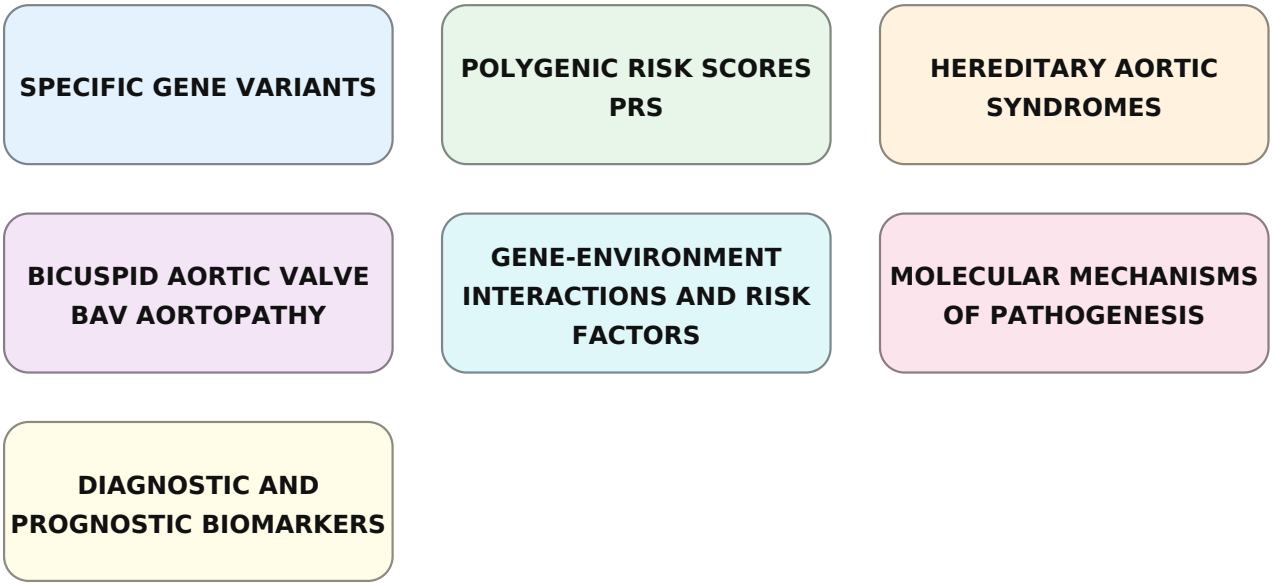


Figure 5. Limitations of current studies (topics)

Figure 6. Future research directions (topics)

MULTI-OMICS INTEGRATION

FUNCTIONAL VALIDATION STUDIES

GENE-ENVIRONMENT INTERACTION STUDIES

LONGITUDINAL COHORT VALIDATION

THERAPEUTIC DEVELOPMENT

GENETIC SCREENING GUIDELINES