PRISMA 2020 Checklist
Chronic Venous Disease and Systemic Vascular Dysfunction: Mechanistic Links and Cardiovascular Associations—A Systematic Review (PROSPERO CRD420261433873)

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Title
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Abstract (structured: Background/Objectives, Methods, Results, Conclusions; registration number, databases, search dates, number of included studies, main results with certainty)
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Section 1 (Introduction), paragraphs 1–3; comparison with previous reviews in Section 4 and Table S13
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Section 1, final paragraph; Section 2.4 (population, evidence domains, comparators, outcomes)
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Sections2.4 and2.8; File S2 Table S4 (eligibility changes and rationale); S4 individual dispositions and17 reports awaiting classification.
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Section 2.2 (MEDLINE/PubMed, Embase, Scopus, CENTRAL; inception to 31 August 2026; searches executed 5 November 2026); File S1 and Table S1
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	File S1, Section 3 (complete strategies for each database, as executed, with limits); Section 2.2
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Section2.3; File S3/Table S3: assisted initial workflow; final eligibility and principal extracted data independently verified for all163 included reports by M.L.D.R.-S. and I.A.D.R., discrepancies resolved by consensus. Expanded excluded-record validation covers521/572, not all572. Historical title-check claims are distinguished from retained validation records.
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Sections2.3 and2.5; S3 oversight and retained prompts; S4 Extraction. Two investigators independently verified principal extracted data for all163 reports; source access comprises95 full texts and68 abstracts. Missing data remain NR; no author correspondence is claimed.
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Sections 2.4 and 2.6 (evidence domains and outcome definitions); Section 2.5
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Section 2.5 (country, setting, data source, period, design, CVeD definition, comparator, sample sizes, follow-up, adjustment, funding); missing information recorded as “NR”
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Section2.7; S3; Table S6; S4 Risk of bias (1390 item judgments, reasons, source locators and derived ratings). All265 previously missing item pointers across56 main reports were reconciled;20 judgments corrected. Unavailable Ge/Levin supplementary methods remain unclear. This item-level documentary reconciliation is distinguished from final independent verification of eligibility/principal data.

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Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Section 2.8 (effect estimates reported as published: hazard, odds, and rate ratios, group means, with 95% CI); Section 2.5
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Sections 2.4 and 2.8 (grouping by evidence domain and outcome); Table S7 (SWiM item 1)
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Section 2.8 (no data conversion or transformation; estimates as published; direction of association coded for each report)
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Section 2.8; Tables 1–4; Figure 1; Figure 2 (forest plot of longitudinal estimates, not pooled); Tables S5 and S11
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Section 2.8 (synthesis without meta-analysis following SWiM; rationale for not pooling); Table S7
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Section 2.8 (qualitative exploration by CEAP class, exposure ascertainment, setting, and overlapping data sources); Table S7 (SWiM item 5)
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Section2.8 and3.11; Table4 and Table S12; S4 Full text sensitivity (outcome-specific all-report and full-text-only composition and interpretation).
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Section 2.8 (publication bias considered within the GRADE-informed certainty assessment); deviation from protocol reported in Table S2
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Section2.8; Table S8; Table4: observational evidence starts low and is downgraded to very low for serious bias. No large-association upgrade is applied. Genetic inference is assessed in a separate framework.
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Section 3.1; Figure 1 (PRISMA flow diagram, including human re-screening and adjudication, reports sought, retrieved, assessed from the abstract only, and not retrieved); File S1, Table S1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Table S9 and S4 Excluded (66 eligibility exclusions), Awaiting classification (17), Retrieval failures (18) and Late duplicate records (2); these dispositions are distinct. Table S4 explains eligibility changes.
Study characteristics	17	Cite each included study and present its characteristics.	Sections 3.3–3.8; Tables 1–3 (systemic vascular function and structure, longitudinal outcomes, genetic studies); Table S5 (cardiovascular disease, linked and overlapping reports) and Table S11 (circulating biomarkers); File S4
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Section3.9; design-specific rating columns in Tables1–3; Table S6 summarizes tools/source availability. All1390 item judgments, reasons and locators are supplied in S4. The265-pointer reconciliation and20 corrections are integrated; inaccessible supplementary methods are explicit.
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Tables1–3 and4; S4 Extraction and Outcome matrix provide report-level values/estimates and source limitations; Table S5 lists clinical contrasts; Table S11 summarizes biomarker patterns. Figure2 displays selected published longitudinal estimates without pooling.
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Sections 3.3–3.9 (characteristics and risk of bias of contributing studies for each domain); Table 4; Table S8

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	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	NA (no meta-analysis); direction and magnitude of associations summarized for each outcome in Sections 3.3–3.8, Figure 2, and Table 4
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Sections 3.5 and 3.6 (differences by CEAP class, setting, exposure definition, and comparator)
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Section 3.11; Table 4 (column “Full-text reports only”); Table S12
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Section 3.10 and Table 4 (publication bias considered in the certainty assessment); no formal statistical assessment
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Section 3.10; Table 4 (summary of findings and GRADE-informed certainty for each outcome); Table S8 (GRADE evidence profile)
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Section 4 (Discussion), paragraphs 1–4; comparison with previous reviews, Table S13
	23b	Discuss any limitations of the evidence included in the review.	Section 4, paragraphs 2–3 and 5 (confounding, reverse causation, detection bias, coding-based exposures, small cross-sectional studies)
	23c	Discuss any limitations of the review processes used.	Section4: post-registration refinements,68 abstract-based reports,51 initial exclusions outside expanded validation, unavailable supplementary methods,17 reports awaiting classification, overlapping sources, absence of pooling and potential publication/reporting bias. Final independent verification of the163 included reports is reported separately.
	23d	Discuss implications of the results for practice, policy, and future research.	Section 4, final paragraph (future research); Section 5 (Implications for Clinical Practice); Section 6 (Conclusions)
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Section 2.1; Abstract (PROSPERO CRD420261433873)
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Section 2.1 (PROSPERO record; no separately published protocol)
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Section 2.1; Table S2 (all amendments with date, justification, and potential influence); Table S4 (eligibility changes during peer review)
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Funding statement (APC funded by Servier; no other external funding)
Competing interests	26	Declare any competing interests of review authors.	Conflicts of Interest statement
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Data Availability Statement; S1 database strategies and flow; S2 protocol/eligibility changes and synthesis summaries; S3 retained prompts and human oversight; S4 report-level extraction, item-level risk of bias, outcome matrix, map and individual selection/validation records.

Locations refer to section, table, and figure numbers of the revised manuscript (Medical Sciences, MDPI template) and its Supplementary Files S1 and S2. NA, not applicable.

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Reconciliation note13 November2026: principal set163 reports (95 full texts/68abstracts),17 awaiting classification; full-text sensitivity in Table S12/S4; model/source and verification limitations explicitly disclosed. A completed location checklist does not certify that the source-documentation limitations have been resolved.