

Flow-Mediated Dilation in Nonmedical Anabolic-Androgenic Steroid Users: A Systematic Review and Meta-analysis Protocol

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Santa Catarina, Brazil.**ADMINISTRATIVE INFORMATION****Support** - No specific funding.**Review Stage at time of this submission** - Preliminary searches.**Conflicts of interest** - None declared.**INPLASY registration number:** INPLASY2026100033**Amendments** - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 7 October 2026 and was last updated on 7 October 2026.**INTRODUCTION**

Review question / Objective Among strength-trained adults, is study-defined current nonmedical anabolic-androgenic steroid (AAS) use associated with lower brachial artery flow-mediated dilation (FMD) compared with never-use of AAS? The primary objective is to quantify the raw mean difference in brachial FMD percentage points between current AAS users and strength-trained or athletic never-users. Secondary objectives are to summarize FMD in former users separately and to describe additional vascular markers only when reported within studies eligible for the FMD review.

Rationale Nonmedical AAS use is common in bodybuilding, strength training, physique enhancement, and performance-enhancement settings. Recent evidence has quantitatively synthesized adverse myocardial remodeling in AAS users, but the vascular consequences, particularly endothelial dysfunction assessed by brachial FMD, have not been synthesized in a dedicated

quantitative review. Comparative FMD studies report heterogeneous findings, potentially reflecting differences in cumulative exposure, current versus former use, exposure ascertainment, comparator selection, and FMD methodology. A focused meta-analysis is therefore warranted. Restricting the primary comparison to strength-trained or athletic never-users is intended to reduce confounding attributable to resistance training itself. FMD will be interpreted as a physiological surrogate of conduit-artery endothelial function, not as a direct cardiovascular-event endpoint. Broader vascular markers will be secondary and will not be used to expand eligibility beyond studies reporting comparative brachial FMD.

Condition being studied The review addresses vascular endothelial function in adults exposed to nonmedical anabolic-androgenic steroids. The focal physiological outcome is brachial artery flow-mediated dilation (FMD), a noninvasive ultrasound measure of conduit-artery endothelial-dependent vasodilator function after reactive hyperemia. The

review will examine whether current nonmedical AAS exposure is associated with impaired FMD compared with never-use in strength-trained adults. FMD is a surrogate vascular phenotype and will not be interpreted as a direct measure of myocardial infarction, heart failure, or cardiovascular mortality.

METHODS

Search strategy Databases: MEDLINE/PubMed, Embase, Scopus, Web of Science Core Collection, SPORTDiscus, and LILACS from inception, with no language/date limits and no design filter. Draft PubMed strategy: (("Anabolic Androgenic Steroids"[Mesh] OR "Anabolic Agents"[Mesh] OR "anabolic androgenic steroid*" [tiab] OR "anabolic-androgenic steroid*" [tiab] OR "anabolic steroid*" [tiab] OR nandrolone [tiab] OR stanozolol [tiab] OR oxandrolone [tiab] OR trenbolone [tiab] OR boldenone [tiab] OR metenolone [tiab] OR methenolone [tiab] OR methandrostenolone [tiab] OR methandienone [tiab] OR oxymetholone [tiab]) AND ("Brachial Artery"[Mesh] OR "Endothelium, Vascular"[Mesh] OR "Vasodilation"[Mesh] OR endothelial [tiab] OR endotheli* [tiab] OR "vascular function" [tiab] OR "vascular dysfunction" [tiab] OR "arterial function" [tiab] OR "flow-mediated dilation" [tiab] OR "flow mediated dilation" [tiab] OR "flow-mediated dilatation" [tiab] OR "flow mediated dilatation" [tiab] OR FMD [tiab] OR "reactive hyperemia" [tiab] OR "reactive hyperaemia" [tiab] OR "arterial reactivity" [tiab] OR "vascular reactivity" [tiab] OR vasodilat* [tiab] OR vasodil* [tiab] OR "arterial stiffness" [tiab] OR "pulse wave velocity" [tiab] OR PWV [tiab] OR "aortic distensibility" [tiab] OR "arterial compliance" [tiab] OR "intima-media thickness" [tiab] OR CIMT [tiab] OR "carotid reactivity" [tiab] OR "coronary plaque" [tiab] OR "coronary artery calcium" [tiab] OR "subclinical atherosclerosis" [tiab])) The strategy will be translated for each database. Backward/forward citation searching, grey-literature searching, and author contact for missing data are planned. The MEDLINE strategy will undergo PRESS-style peer review before the formal search is frozen; full executed strategies, dates, interfaces, and result counts will be reported according to PRISMA-S.

Participant or population Adults aged 18 years or older. The primary synthesis will focus on strength-trained, resistance-trained, bodybuilding, or athletic populations. Studies with mixed pediatric/adult samples will be eligible only when adult data are separable or all participants in the relevant comparison are adults. Any sex will be eligible.

Participant characteristics relevant to confounding, including age, smoking/nicotine exposure, blood pressure, body size/composition, lipid profile, training exposure, and concomitant vasoactive, performance-enhancing, or recreational drug use, will be extracted when reported.

Intervention This is an exposure-based systematic review, not a researcher-assigned intervention review. The exposure is nonmedical or supraphysiologic anabolic-androgenic steroid use for physique enhancement, bodybuilding, strength/performance enhancement, or recreational purposes. Eligible ascertainment includes biochemical testing, anti-doping data, medical records, structured interview, or clearly defined self-report. The primary exposure group is study-defined current AAS use, which may include temporary between-cycle periods within an ongoing/recurrent pattern when classified as current by the source study. Former users with sustained cessation will be analyzed separately. Therapeutic testosterone replacement or prescribed androgen use for medical indications will be excluded.

Comparator Primary comparator: strength-trained or athletic adults with no prior AAS use. When multiple compatible athletic never-user groups are available, they will be combined using standard methods. Secondary comparators may include sedentary or general-population never-users, but these will be analyzed separately and will not be mixed with athletic controls in the primary effect estimate. Studies without a non-AAS comparator are excluded from the formal systematic review.

Study designs to be included Analytical cross-sectional studies, prospective or retrospective cohort studies, and case-control studies providing comparative standard brachial FMD data, or sufficient data to derive conventional FMD%. Case reports/series, animal or in-vitro studies, editorials, reviews, and comparative vascular studies without eligible brachial FMD will be excluded.

Eligibility criteria Include adults (≥ 18 years) with nonmedical AAS exposure and a non-AAS comparator. Formal eligibility requires comparative standard brachial artery FMD reported as percent diameter change after reactive hyperemia, or sufficient data to derive conventional FMD%. Current, on-cycle, temporarily between-cycle, former, or cumulative exposure may be reported, but the primary analysis will use study-defined current users; former users with sustained cessation will remain separate. Never-users are required as the comparator; strength-trained/

athletic controls are preferred for the primary synthesis. Eligible designs are analytical cross-sectional, cohort, and case-control studies. Therapeutic testosterone replacement or androgens prescribed for hypogonadism, cachexia, anemia, delayed puberty, or other medical indications will be excluded. Case reports, case series, reviews, editorials, animal/in-vitro studies, and studies without eligible FMD are excluded. Peer-reviewed reports and sufficiently detailed dissertations, preprints, or conference reports with unique comparative data may be included; non-peer-reviewed reports will be excluded in sensitivity analysis. No language or publication-date restrictions will apply. Multiple reports from overlapping cohorts will be mapped to one underlying cohort and participants will not be double-counted within any pooled outcome.

Information sources MEDLINE via PubMed, Embase, Scopus, Web of Science Core Collection, SPORTDiscus, and LILACS will be searched from inception to the final search date without language restrictions. Additional sources will include backward reference searching and forward citation searching of included studies and relevant reviews; dissertation/thesis repositories; preprint platforms; conference records indexed in bibliographic databases; and observational study registries when relevant. Corresponding authors will be contacted for missing or unclear numerical data. Searches will be updated before manuscript submission if more than six months have elapsed since the initial formal search.

Main outcome(s) Primary outcome: brachial artery flow-mediated dilation (FMD), expressed as percent change in arterial diameter from baseline after reactive hyperemia. When both peak FMD and a fixed-time estimate are reported, peak FMD will be preferred; when a study prespecifies one conventional FMD measure as its primary vascular outcome, that measure will be used unless incompatible with the review definition. The primary effect measure is the raw mean difference in FMD percentage points between study-defined current AAS users and strength-trained/athletic never-users; negative values indicate lower FMD in AAS users. Repeated measurements from the same participants will not be treated as independent observations.

Additional outcome(s) Secondary outcomes, extracted only from FMD-eligible studies, include: FMD among former users with sustained cessation versus never-users; FMD in actively on-cycle versus temporarily between-cycle current users when separable; endothelium-independent

vasodilation; pulse-wave velocity; carotid intima-media thickness; aortic/carotid stiffness, compliance, or distensibility; carotid artery reactivity; and coronary artery calcium or plaque measures. Distinct vascular constructs will not be collapsed into a single omnibus standardized effect. Secondary outcomes will generally be pooled only when at least three independent studies provide sufficiently compatible definitions and units.

Data management Search results will be exported to reference-management software, deduplicated using automated and manual methods, and imported into a systematic-review screening platform. Reviewers will complete a calibration exercise before formal screening. Two reviewers will independently screen titles/abstracts and full texts; disagreements will be resolved by discussion or third-reviewer adjudication. Full-text exclusion reasons will be recorded. A standardized piloted extraction form will be used. Two reviewers will independently extract all primary-outcome numerical data and independently verify study characteristics, exposure definitions, secondary outcomes, and transformations. Multiple reports will be linked to one underlying cohort. Missing or unclear data will prompt author contact. Feasibility-stage numerical entries will not be carried forward without de novo re-extraction after registration. Analysis code and the de-identified final extracted dataset will be retained and shared when permitted.

Quality assessment / Risk of bias analysis Risk of bias will be assessed independently by two reviewers, with consensus or third-reviewer adjudication. Analytical cross-sectional studies will use the revised JBI risk-of-bias tool for analytical cross-sectional studies; case-control studies will use the JBI case-control tool; longitudinal follow-up exposure studies will use ROBINS-E. Particular attention will be paid to participant selection, AAS exposure ascertainment, confounding, and FMD measurement. A prespecified confounding set includes age, smoking/nicotine exposure, blood pressure/hypertension, body size/composition, lipid profile, resistance-training exposure, and concomitant vasoactive, performance-enhancing, or recreational drug use. Risk-of-bias judgments will inform sensitivity analyses and interpretation. Certainty of evidence will be assessed by outcome using GRADE principles adapted to observational exposure/risk-factor evidence.

Strategy of data synthesis The primary synthesis will compare study-defined current AAS users with strength-trained/athletic never-users. Compatible

FMD results will be pooled as raw mean differences in percentage points with 95% confidence intervals. Random-effects meta-analysis will use restricted maximum likelihood (REML) for between-study variance and the modified Knapp-Hartung safeguard $q^* = \max(1, q)$ for the primary confidence interval; conventional REML-Wald inference will be a sensitivity analysis. Heterogeneity will be described using tau-squared, I-squared, and Cochran Q; a 95% prediction interval will be reported only when at least five independent studies contribute and it is statistically interpretable. Means/SDs will be used directly; SE will be converted to SD, and validated quantile-estimation methods will be used for medians/IQR only when distributional assumptions are defensible. Clearly skewed data will not be forced into mean-based synthesis. Repeated or overlapping observations will not be double-counted. If quantitative synthesis is inappropriate, structured narrative synthesis will be used.

Subgroup analysis Prespecified potential effect modifiers include duration/cumulative AAS exposure, objective versus self-reported exposure ascertainment, comparator type, actively on-cycle versus temporarily between-cycle current use, former use with sustained cessation, cuff location, peak versus fixed-time FMD, and key FMD protocol characteristics. Former users will remain a separate exposure category. Subgroup analyses will be undertaken only when sufficient independent studies and within-subgroup data are available. Formal meta-regression will be performed only if at least 10 independent studies are available per candidate covariate with adequate between-study variation. Otherwise, potential effect modifiers will be explored descriptively and through limited prespecified subgroup analyses without significance-driven interpretation.

Sensitivity analysis Prespecified sensitivity analyses will: exclude studies requiring median/IQR-to-mean/SD conversion; restrict to objective/biochemical AAS exposure verification; restrict to participants confirmed actively on-cycle at FMD testing when separable; restrict to strength-trained/athletic comparators; exclude studies with important risk-of-bias concerns; perform leave-one-out analyses; exclude non-peer-reviewed reports; and compare conventional REML-Wald inference with the primary modified Knapp-Hartung approach. Alternative eligible current-use time points will also be examined when repeated measurements are available in the same participants.

Language restriction No language restrictions will be applied.

Country(ies) involved Brazil.

Other relevant information The project is being registered prospectively at the preliminary-search stage. Before registration, a targeted feasibility exercise identified sentinel studies and recorded selected published summary statistics solely to determine whether quantitative synthesis was viable. Formal eligibility screening, de novo duplicate extraction, risk-of-bias assessment, and final analysis have not started. All feasibility-stage numerical values will be independently re-extracted under the registered protocol. A targeted check of INPLASY, PROSPERO, major bibliographic databases, and recent review literature did not identify a registered or published systematic review/meta-analysis specifically pooling brachial FMD in nonmedical AAS users. The search will be validated against known sentinel eligible studies before it is frozen. Any substantive post-registration changes will be documented as protocol amendments and deviations will be identified in the final report.

Keywords anabolic-androgenic steroids; flow-mediated dilation; endothelial dysfunction; bodybuilding; vascular function; meta-analysis.

Dissemination plans Results will be submitted to a peer-reviewed cardiovascular, sports-medicine, or clinical pharmacology journal and may be presented at a scientific meeting. The completed review will report the INPLASY registration number and DOI and will explicitly describe any protocol deviations. Full database search strategies, study-level extraction tables, risk-of-bias assessments, and statistical code will be provided as supplementary material or deposited in a public repository when permitted. The final analytic dataset will be shared in de-identified form when licensing and source-report restrictions allow.

Contributions of each author

Author 1 - Alessandro Meneghetti Anversa - Conception and design; data acquisition; data analysis and interpretation; statistical analysis; manuscript drafting; critical revision for important intellectual content.

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