Sriwijaya Journal of Internal Medicine
https://phlox.or.id/index.php/sjim
e-ISSN: 2988-3237
Vol. 4 No. 2 (2026): 137–151

SYSTEMATIC REVIEW & META-ANALYSIS

Circulating Asymmetric Dimethylarginine in Adults with Essential Hypertension Compared with Normotensive Controls: A Systematic Review and Meta-Analysis

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ARTICLE INFO

Article history
Received: July 20, 2026
Revised: August 18, 2026
Accepted: September 8, 2026
Available online: September 15, 2026
Published: September 16, 2026

Keywords:
Asymmetric dimethylarginine
Endothelial dysfunction
Essential hypertension
Meta-analysis
Nitric oxide

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DOI
https://doi.org/10.59345/sjim.v4i2.343

ABSTRACT

Background: Asymmetric dimethylarginine (ADMA) is an endogenous nitric oxide synthase inhibitor and a candidate mediator of the endothelial dysfunction accompanying raised arterial pressure. Prior meta-analyses covered coronary disease, heart failure, chronic kidney disease and preeclampsia, but none quantified the essential hypertension versus normotension contrast.

Objective: To quantify the difference in circulating ADMA between adults with essential hypertension and normotensive controls, and to characterise its clinical and methodological moderators.

Methods: MEDLINE and Europe PMC were searched for studies of circulating ADMA in essential hypertension with a concurrent normotensive group. Effect sizes for paywalled reports publishing only a direction and p-value were recovered from test statistics and group sizes, graded into three tiers, with non-significant results entered as zero. Hedges g was pooled under a random-effects model (REML, Knapp–Hartung); bias was appraised with the Newcastle–Ottawa Scale.

Results: Twenty-four studies contributed 2,201 participants (1,293 hypertensive, 908 normotensive). ADMA was higher in essential hypertension, Hedges g = 0.642 (95% CI 0.340 to 0.945; p = 0.0002), with I^2 = 81.4% and a 95% prediction interval (−0.673 to 1.957) including zero. Directly readable studies gave g = 0.972 and recovered studies g = 0.330 (interaction p = 0.019). Small-study effects were present (Begg p = 0.029; trim-and-fill g = 0.407), yet the estimate stayed positive across all 39 sensitivity specifications.

Conclusion: The plausible effect is about 0.33 to 0.64 standardised units, roughly 0.1 micromoles per litre. Certainty is very low and the distributions overlap too much for ADMA to discriminate between individuals.

1. Introduction

Hypertension remains the single largest modifiable contributor to the global burden of cardiovascular disease. Pooled analyses of more than a thousand population-representative surveys have shown that the number of adults living with hypertension doubled between 1990 and 2019, and that the burden has shifted decisively towards low-income and middle-income countries, where diagnosis and control rates remain lowest[1]. The same collaboration has since demonstrated that the association between adiposity and raised blood pressure differs substantially between world regions, which argues against treating the pathophysiology of hypertension as uniform across populations[2]. For clinicians practising in Southeast Asia, that regional heterogeneity is not an abstraction: it bears directly on which mechanistic pathways are worth measuring and which are not. The gap is one of control rather than of knowledge: modelling of global treatment targets indicates that meeting them would avert tens of millions of deaths[3], a cluster-randomised trial in rural China has shown that village-doctor-led care can achieve control at scale[4], and supplying home monitors improves control in low-income patients[5]. What remains unsettled is the mechanism, and which of its measurable intermediates is worth the cost of assay.

Endothelial dysfunction sits close to the centre of most mechanistic accounts of essential hypertension. Reduced bioavailability of nitric oxide raises vascular tone, impairs flow-mediated dilatation and promotes vascular remodelling, and the pathways that regulate nitric oxide synthesis have accordingly attracted sustained attention as therapeutic targets. Recent work has shown that mitochondrial cyclophilin D acetylation promotes endothelial dysfunction and raises blood pressure in experimental models[6], that shear-stress signalling through endothelial HEG1 regulates vascular tone and arterial pressure[7], and that circulating metabolites which trigger vascular dysfunction track with blood pressure in large multiethnic cohorts[8]. Amino-acid transport and the gut microbiome have both been shown to modulate arterial pressure, through inhibition of the transporter SLC38A2[9] and through a microbial metabolite that alters salt sensitivity[10]. Asymmetric dimethylarginine (ADMA) occupies a distinctive position within this literature because it is not merely a marker of endothelial injury but a direct competitive inhibitor of all three nitric oxide synthase isoforms.

e-ISSN: 2988-3237
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ADMA is generated by proteolysis of methylated arginine residues and cleared principally by dimethylarginine dimethylaminohydrolase and by renal excretion. Its biology has been clarified considerably in the past five years. A multicentre consortium established that the second isoform, DDAH2, does not in fact hydrolyse ADMA, so clearance depends on DDAH1 and the kidney[11]; mechanical force has been shown to promote DDAH1-mediated hydrolysis of ADMA[12]; and renal function has been shown to underpin the cyclooxygenase-2 to ADMA axis in both mice and humans[13]. At the level of the resistance vessel, ADMA enables depolarising spikes and vasospasm in mesenteric and coronary arteries, which supplies a direct route from raised ADMA to raised vascular tone[14]. Clinically, higher ADMA has been linked to reduced myocardial mechano-energetic efficiency in hypertensive subjects[15], to progression of kidney disease[16], and to vascular injury in inflammatory disease[17]. Loss of DDAH1 raises ADMA and worsens blood-brain barrier injury after ischaemia[18], and arginine methylation by PRMT1, the enzyme that generates ADMA, has measurable effects on vascular protein secretion[19]. Yet a competing observation complicates the picture: in chronic kidney disease, impaired vascular function has been shown to track with symmetric rather than asymmetric dimethylarginine[20], and biopterin availability modifies the relationship between ADMA and peripheral microvascular function[21].

Against this background the primary clinical question is disarmingly simple and has never been answered quantitatively: by how much, if at all, does circulating ADMA differ between adults with essential hypertension and normotensive people? A search of the meta-analysis publication type conducted for this review returned 49 syntheses concerning asymmetric dimethylarginine, covering coronary artery disease, heart failure, peripheral arterial disease, chronic kidney disease, preeclampsia, gestational diabetes, rheumatic disease, critical illness, neurovascular disease, migraine, schizophrenia and all-cause mortality, and the effect of statins or arginine supplementation on ADMA concentration. Not one takes essential hypertension as the index condition; the nearest, a synthesis of the plasma ADMA reference range, pools values across healthy populations without a hypertensive comparison. **The novelty of this study lies in** being the first quantitative synthesis of the hypertensive-versus-normotensive ADMA contrast, and in the method used to assemble it: rather than discarding the substantial body of older reports that publish only a direction of effect and a p-value, this review recovers their standardised effect sizes from the statistics their authors did publish, grades each recovery by transparency, and enters non-significant results as zero. That decision is not a technical footnote. The studies whose numbers are hardest to obtain turn out to be disproportionately the null ones, so recovering them changes both the pooled estimate and what can honestly be claimed about it. **The aim of this study was to** quantify the difference in circulating ADMA between adults with essential hypertension and normotensive controls, to determine how much of the between-study variation is attributable to clinical and methodological moderators rather than to biology, and to establish whether the association survives formal adjustment for small-study effects.

2. Methods

2.1. Reporting and protocol

This systematic review and meta-analysis was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 statement[22]. All analytical decisions described below, including the effect-size recovery procedure and the pre-specified sensitivity analyses, were fixed before the pooled estimate was computed, and the complete analytical record, including every intermediate result file, has been retained. The full Boolean search strings, with field tags and the interface each was executed against, are provided in the supplementary appendix so that the search can be reproduced exactly.

2.2. Eligibility criteria

Studies were eligible if they reported an original comparison of circulating ADMA concentration between adults with essential or primary hypertension and a concurrently recruited normotensive comparison group. Hypertension could be defined by office, home or ambulatory blood pressure measurement, or by current antihypertensive drug use. ADMA had to be measured in plasma or serum by a validated method. Case-control, cross-sectional and pre-randomisation baseline comparisons were all admissible. No language restriction and no date restriction were applied, because the earliest reports of ADMA in hypertension date from the late 1990s and excluding them would have biased the pooled estimate towards the modern assay platforms.

Studies were excluded when the index population was secondary or endocrine hypertension, pulmonary hypertension, portal hypertension or a hypertensive disorder of pregnancy, all of which have distinct vascular biology and, in the case of primary aldosteronism, a distinct cardiovascular risk profile even in its subclinical form[23]; when the population was defined by an overriding comorbidity that independently raises ADMA, such as dialysis, transplantation or established coronary disease, unless an uncomplicated hypertensive subgroup was separately reported; and when the participants were children. Where a study reported an eligible essential hypertension arm alongside ineligible arms, only the eligible arm and its matched comparison group were extracted. Three included reports fall into this category and their provenance is recorded in the characteristics table: one is principally a study of white-coat hypertension, from which the sustained hypertensive and normotensive arms were taken; one is principally a comparison of two antihypertensive agents, from which only the pre-treatment baseline contrast was taken; and one is principally an investigation of polycystic kidney disease, from which the hypertensive comparison arm and the healthy control arm were taken.

2.3. Information sources and search

MEDLINE was searched through the PubMed E-utilities interface and Europe PMC through its REST interface, including its open-access full-text index. Search strings combined controlled and free-text terms for asymmetric dimethylarginine with terms for essential, primary, arterial, newly diagnosed and untreated hypertension, and with terms for normotensive, healthy or control comparison groups. The Europe PMC full-text index was mined programmatically: candidate records were retrieved in bulk, their open-access full texts parsed, and group-level ADMA values extracted from result tables and result-section prose that no abstract-level search would reach. This step recovered several of the studies with directly reported means and is described in sufficient detail in the supplementary appendix to be repeated. Reference lists of retrieved reports and of previous ADMA syntheses in adjacent fields were screened by hand.

2.4. Study selection and data extraction

Records were screened on title and abstract and then assessed in full. For each included study the following were extracted: country, design, setting, case definition, treatment status, sample matrix, assay platform, group sizes, and the mean and dispersion of ADMA in each group. Where a study reported a median with an interquartile range rather than a mean with a standard deviation, the mean and standard deviation were estimated from the median, the quartiles and

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the group size by the quantile-based method of Wan and colleagues. Where dispersion was published as a standard error of the mean, it was converted by multiplying by the square root of the group size. Two studies printed ADMA in millimoles per litre, which is roughly three orders of magnitude above the physiological range and is evidently a unit error; because a purely multiplicative scale error cancels in the numerator and the denominator of a standardised difference, this does not affect the pooled estimate, and the values were used as published with the discrepancy recorded. The two Chinese-language reports were entered from their English abstracts by the recovery route described below; no translation of the full texts was obtained, and neither full text was read. Smoking status, which alters circulating methylarginine concentrations[24], was reported too inconsistently across the included studies to be extracted.

Two decisions of substance were taken at extraction. One report was found to publish the same Sofia hypertensive and control arms, with identical means and dispersions, as a study already included; it was excluded as a duplicate cohort to prevent double counting. A second report gave a standard deviation an order of magnitude tighter than every other study in the field and below the reproducibility of the assay itself; it was judged internally implausible and excluded. Two reports from the same Italian hypertension unit used the same forearm blood-flow protocol and may share participants; both were retained and a pre-specified sensitivity analysis removes the earlier and smaller of the two. The asymmetry between this decision and the exclusion above should be explicit. The excluded report published means and dispersions identical to those of an included study, which is demonstrated duplication; the two Italian reports share a unit and a protocol, which is possible overlap that neither publication states. Were they to overlap, the more damaging part would be the control arms of eight and twenty-one, since the smaller could be wholly contained in the larger. Retention with a sensitivity analysis, rather than exclusion, was chosen because exclusion on suspicion would set a standard the rest of the pool could not meet; the specification that removes the earlier report gives 0.639.

Two further values were flagged rather than excluded, and the reasoning should be explicit because it differs from the reasoning that excluded the report with an implausible dispersion. In one Turkish cohort the control mean is 0.318 micromoles per litre, below the usual plasma range and reported to four significant figures. In one Chinese cohort the control value differs between the abstract and the results section, and the printed unit is wrong. In both cases the anomaly lies in a single reported figure that can be bounded, and the effect of the anomaly can be measured by removing the study; in the excluded report the anomaly lay in the dispersion, which is the denominator of the effect size, so no bound was available and no sensitivity analysis could contain it. The corresponding authors were not contacted, which is a limitation.

2.5. Effect measure and recovery of effect sizes

The standardised mean difference, expressed as Hedges g, was the effect measure throughout. This choice is a positive methodological statement rather than a convenience. ADMA is reported in micromoles, nanomoles and millimoles per litre across four assay platforms whose absolute calibrations are not interchangeable; a comparison of two quantification methods has shown systematic differences between platforms even when precision is acceptable[25]. Three included studies report concentrations four to eight times those of the modern reference range, consistent with the chromatographic methods in use when they were performed. A raw mean difference across such a mixture would have no interpretable unit.

A substantial part of the older literature on this question is paywalled and publishes only the direction of an effect and a p-value or p threshold. Discarding those reports would not have been a neutral act, because they are disproportionately the null and near-null results; excluding them biases the pooled estimate upward. For every such study the standardised mean difference was therefore recovered from the statistics the authors did publish, using the standard identity relating the standardised mean difference to the two-sample t statistic and the group sizes, as set out in the Cochrane Handbook[26]. Written out, the recovered effect size d equals t multiplied by the square root of the quantity one over n_1 plus one over n_2, where n_1 and n_2 are the hypertensive and normotensive group sizes and t is the two-sample statistic implied by the published p-value on n_1 plus n_2 minus two degrees of freedom. Hedges g was then obtained from d by the exact small-sample bias correction. Each recovered value is a deterministic function of numbers printed in the published report: the p-value or threshold and the two group sizes. No mean and no standard deviation was guessed.

Recoveries were graded into three tiers and the tier of every study was recorded. In tier 1 an exact p-value is published, so the effect size is fully determined. In tier 2 a threshold is published, such as p below 0.05, 0.01 or 0.0001; the threshold itself was used, which yields the smallest effect compatible with what the authors reported and is therefore a genuine lower bound. In tier 3 the difference is reported as non-significant, or only a direction is given with no p-value at all; these were entered as zero.

The status of the tier 3 convention needs to be stated precisely, because it is the load-bearing assumption of this review and it is weaker than the tier 2 convention in two distinct ways. First, it is not a bound. A study reporting a non-significant difference has a true effect that could be positive or negative, so entering zero is a choice of central tendency, not a limit; it biases towards the null only under the assumption that the underlying effects in those studies are on average positive, which is part of what the review is trying to establish. The direction of the assumption is the conservative one, but the argument is circular and is presented here as such. Second, and more consequentially, the convention is conservative for the location of the estimate but not for its scale. A tier 3 study enters with a variance computed from its group sizes alone, as though a zero had been measured with the full precision the sample size permits, so these studies contribute to narrowing the confidence interval on the strength of no published effect size. The magnitude of that contribution is quantified in the Results.

Two pre-specified sensitivity analyses test the tier 2 convention directly by reading every threshold at half and at twice the stated p-value, and a third removes the tier 3 studies altogether.

2.6. Risk of bias

Risk of bias was appraised with the Newcastle-Ottawa Scale, which is the appropriate instrument because every included study is an observational comparison rather than a randomised or non-randomised intervention; RoB 2.0 and ROBINS-I do not apply to this evidence base. Five domains were rated: representativeness and case definition; selection and definition of controls; comparability through matching or adjustment; ascertainment of exposure through the ADMA assay; and non-response rate and sample adequacy. Star counts were recorded alongside a domain-level judgement of low risk, some concerns or high risk. Studies whose effect size was recovered from the abstract were appraised from the abstract alone; their ratings are capped at some concerns by default and they are marked as recovered in the risk-of-bias display. Because the two groups differ in what could be appraised rather than in what was done, their star counts are

e-ISSN: 2988-3237
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not strictly commensurable, and this is stated wherever the counts are quoted. Certainty in the pooled estimate was assessed post hoc across the standard domains of study design, risk of bias, inconsistency, indirectness, imprecision and publication bias.

2.7. Statistical analysis

Hedges g and its variance were computed for each comparison using exact bias-correction formulae. Estimates were pooled under a random-effects model with the between-study variance estimated by restricted maximum likelihood and confidence intervals derived with the Knapp-Hartung adjustment, which is appropriate when the number of studies is moderate and heterogeneity is substantial. Heterogeneity was quantified by the between-study variance with its Q-profile confidence interval, by the ratio of that variance to total variance, and by Cochran Q; a 95% prediction interval was computed to express the range within which the effect in a new setting would be expected to lie. Subgroup analyses were performed by effect source, treatment status, sample matrix, publication era, study size, assay platform and region, with the interaction assessed by the between-groups Q statistic. Mixed-effects meta-regression was fitted for effect source, publication year, assay platform, log transformed total sample size, and a joint model of year and sample size.

Thirty-nine sensitivity specifications were pre-specified: a complete leave-one-out series; removal of each flagged study individually and together; removal of the possible cohort overlap; restriction to established essential hypertension, to untreated cohorts and to chromatographic assays; restriction to directly reported and to recovered data separately; exclusion of the tier 3 recoveries; the two threshold-reading conventions described above; alternative between-study variance estimators; removal of the Knapp-Hartung adjustment; and a fixed-effect model. Small-study effects were assessed by Egger regression and by Begg rank correlation, and a trim-and-fill procedure was used to obtain a bias-adjusted estimate. All analyses were performed in R.

3. Results

3.1. Study selection

The searches returned 2,553 records, 920 from MEDLINE and 1,633 from Europe PMC. After 174 duplicates were removed, 2,379 records were screened on title and abstract, 195 reports were sought for retrieval and 150 were assessed in full. Twenty-four studies met all eligibility criteria and were included: twelve contributed directly reported means and standard deviations, and twelve contributed effect sizes recovered from published test statistics. Only fourteen otherwise eligible reports were finally lost because they carried neither extractable summary data nor any recoverable statistic; had the recovery procedure not been used, that figure would have been twenty-six. The complete selection pathway, from the records identified in each database through to the twenty-four studies pooled, is detailed in Figure 1.

Six reports were excluded at full assessment for reasons of substance rather than data availability. One duplicated a cohort already included; one reported an internally implausible dispersion; one compared hypertensive patients with and without left ventricular diastolic dysfunction and so had no normotensive arm; one studied newly diagnosed type 2 diabetes rather than hypertension; one studied obstructive sleep apnoea; and one was a paediatric population. These six exclusions, together with the counts excluded at each earlier step, are itemised in the eligibility boxes of Figure 1.

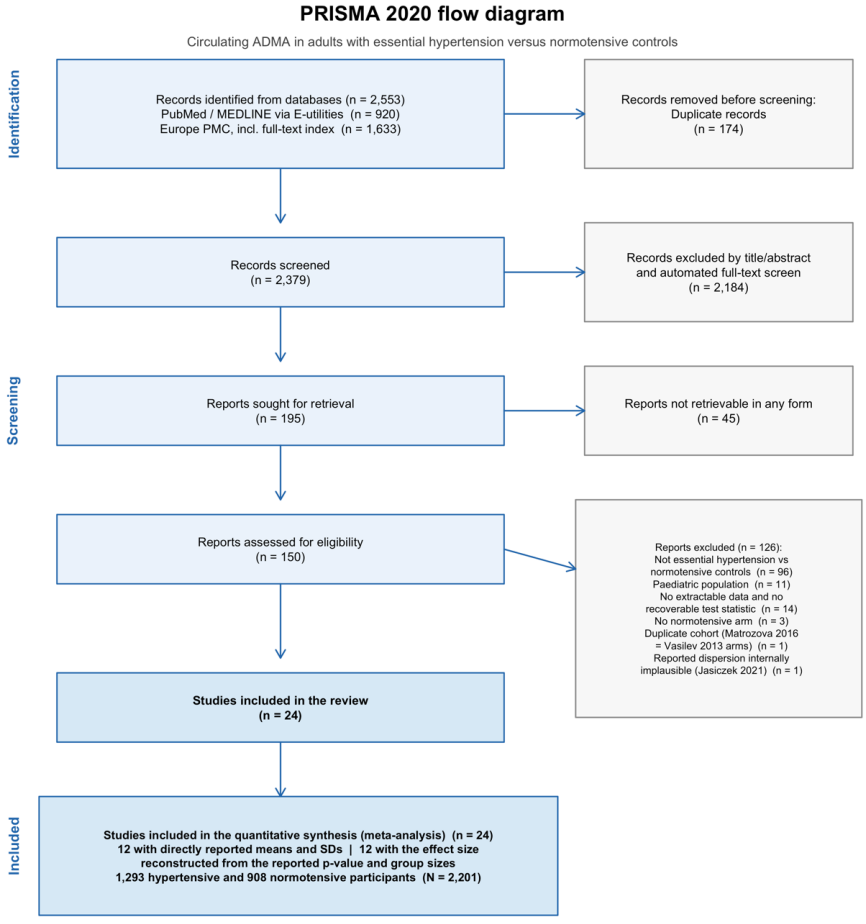

Figure 1. PRISMA 2020 flow diagram for study selection. Records were identified through MEDLINE and Europe PMC.

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3.2. Characteristics of the included studies

The twenty-four included studies were published between 1999 and 2022 and contributed 2,201 participants, 1,293 with essential hypertension and 908 normotensive controls. That total requires one qualification that is easily lost: 1,192 of those participants belong to studies whose group means and dispersions were measured and read, while 1,009 belong to studies that contributed only a p-value and two group sizes. A recovered study supplies one number and nothing else, so it cannot enter any analysis of absolute concentration and its participants are counted rather than observed. Eleven studies were conducted in Europe or Australia and thirteen in Asia or Africa. Twelve cohorts were untreated or drug naive at the time of sampling and twelve were mixed or treated. Sixteen studies measured ADMA in plasma and eight in serum; seventeen used a chromatographic platform and seven an immunoassay. Twenty-one of the twenty-four enrolled fewer than one hundred participants in total, and only three exceeded that threshold, as the total-n column of Table 1 shows. The case definition was not uniform: alongside twenty studies of established essential hypertension, the pool contains a cohort of young men with borderline hypertension, a hypertensive arm that includes twenty-six prehypertensive participants within its sixty, an exclusively elderly cohort compared against age-matched elderly healthy volunteers, and a hypertensive group assembled to serve as a comparator in a study of polycystic kidney disease. Five cohorts enrolled men only. Three further features of the pool bear on how far it generalises. Two countries supply almost half of it, six studies being Turkish and five Chinese, while the remaining thirteen come from eleven different countries contributing one or two each; the Asia and Africa stratum used in the subgroup analysis is eleven Turkish and Chinese studies plus two others, so that contrast should be read as those two countries against Europe rather than as a general geographical hypothesis. The allocation ratio varies thirteenfold, from 0.34 hypertensive participants per control in the borderline cohort, which enrolled three times as many controls as cases, to 4.50 in the smaller Italian study with thirty-six cases and eight controls; because the variance of a standardised difference depends on the harmonic mean of the two group sizes, severely unbalanced studies contribute less information than their enrolment suggests. And the evidence base is old: twelve of the twenty-four studies were published before 2010 and only four since 2020. The country, design, group sizes, case definition, treatment status, sample matrix, assay platform and effect source of every included study are detailed in Table 1.

Table 1. Characteristics of the twenty-four included studies. HT denotes hypertensive participants and NT normotensive controls. Tier 1 to tier 3 denote the transparency grade of studies whose effect size was recovered from published test statistics rather than read directly.

Study	Country	n HT	n NT	Total n	Case definition	Treatment	Matrix	Assay	Effect source
Surdacki 1999[27]	Poland	19	11	30	Established EH, men	Untreated	Plasma	HPLC	Reported
Holm 2002[28]	Norway	39	25	64	Established EH	Mixed	Plasma	HPLC	Tier 3
Paiva 2002[29]	Finland	16	47	63	Borderline HT, men	Untreated	Plasma	HPLC	Reported
Kielstein 2003[30]	Germany	24	24	48	Established EH, elderly	Mixed	Plasma	HPLC	Reported
Schlaich 2004[31]	Australia	12	15	27	Established EH	Mixed	Plasma	HPLC	Tier 3
Curgunlu 2005[32]	Turkey	34	34	68	Established EH	Untreated	Plasma	HPLC	Reported
Perticone 2005[33]	Italy	36	8	44	Established EH	Never treated	Plasma	HPLC	Tier 2
Tsuda 2005[34]	Japan	38	35	73	Established EH, men	Mixed	Plasma	HPLC	Tier 3
Zhang 2005[35]	China	42	23	65	Established EH	Newly diagnosed	Serum	HPLC	Tier 2
Xie 2006[36]	China	41	20	61	Established EH	Untreated	Serum	ELISA	Tier 2
Atamer 2008[37]	Turkey	34	38	72	Established EH	Newly diagnosed	Serum	HPLC	Tier 3
Wang D 2009[38]	Denmark	9	10	19	Established EH	Mixed	Plasma	HPLC	Reported
Perticone 2010[39]	Italy	63	21	84	Established EH	Untreated	Plasma	HPLC	Tier 2
Sonmez 2010[40]	Turkey	30	30	60	Established EH, men	Newly diagnosed	Plasma	HPLC	Tier 1
Wang 2011[41]	China	60	26	86	Includes prehypertension	Mixed	Plasma	LC-MS	Reported
Karadurmus 2012[42]	Turkey	51	37	88	Established EH	Never treated	Plasma	EIA	Reported
Gonenc 2013[43]	Turkey	38	22	60	Established EH	Mixed	Serum	ELISA	Tier 2
Vasilev 2013[44]	Bulgaria	18	18	36	Established EH	Mixed	Serum	ELISA	Reported
Xia 2015[45]	China	182	182	364	Established EH	Never treated	Plasma	HPLC	Tier 2
Gkaliagkousi 2018[46]	Greece	165	71	236	Established EH	Drug naive	Plasma	HPLC	Reported
Gamil 2020[47]	Sudan	260	144	404	Established EH	Mixed	Serum	LC-MS	Reported
Charkiewicz 2021[48]	Poland	20	15	35	Established EH, men	Mixed	Serum	ELISA	Tier 3
Ekinci 2021[49]	Turkey	20	12	32	Established EH	Mixed	Serum	ELISA	Reported
Ni 2022[50]	China	42	40	82	Established EH	Mixed	Plasma	ELISA	Reported
Total		1293	908	2201					

EH, essential hypertension; HPLC, high-performance liquid chromatography; LC-MS, liquid chromatography with tandem mass spectrometry; ELISA and EIA, enzyme immunoassay. Tier 1, exact p-value published; tier 2, p threshold published; tier 3, non-significant or direction only. Three studies contributed an eligible arm from a report whose primary question was different: Curgunlu 2005 (white-coat hypertension), Xie 2006 (comparison of two antihypertensive agents, baseline contrast only) and Ekinci 2021 (polycystic kidney disease). Ni 2022 is principally a laboratory study of profilin-1 signalling with a preliminary clinical arm, and Kielstein 2003 addressed renal perfusion in ageing.

3.3. Risk of bias

Newcastle-Ottawa star counts ranged from five to eight of a possible nine, with a median of six. Six studies scored eight stars, two scored seven, nine scored six and seven scored five. No study was rated at low risk of bias overall: nine were judged at high risk and fifteen raised some concerns. The commonest reason for a high-risk rating was sample adequacy, and the studies affected are among the smallest in the set, one contributing nineteen participants in total[38], one eight controls[33], one twelve controls[49] and one fifteen[48]. Case definition accounted for two further high-risk ratings: one study enrolled borderline rather than established hypertension[29], and one included a prehypertensive subgroup within its hypertensive arm[41]. One study was downgraded on comparability because its sex distribution differed markedly between groups[37], with seven men among thirty-four cases and twenty among thirty-eight controls. The judgement in each of the five domains for every study, together with its star count, is detailed in Figure 2.

e-ISSN: 2988-3237
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These counts should be read with one qualification. Twelve studies were appraised from a full text and twelve from an abstract alone, and the star count measures what could be read as much as what was done. The effect is visible in the distribution: six of the seven studies scoring five stars are studies whose effect size was recovered from an abstract. The two groups are therefore not strictly commensurable, and no inference about the relative quality of recovered and directly reported studies should be drawn from the star counts alone.

Figure 2. Risk-of-bias traffic-light plot using Newcastle-Ottawa domains. Domain 1, representativeness and case definition; domain 2, selection and definition of controls; domain 3, comparability through matching or adjustment; domain 4, ascertainment of exposure through the ADMA assay; domain 5, non-response rate and sample adequacy. Green with a plus denotes low risk, amber with a dash some concerns and red with a cross high risk. Studies annotated as reconstructed had their effect size recovered from the published abstract and were appraised from the abstract alone. Newcastle-Ottawa star counts are shown at the right.

3.4. Primary meta-analysis

Across the twenty-four studies, circulating ADMA was higher in adults with essential hypertension than in normotensive controls, with a pooled Hedges g of 0.642 (95% CI 0.340 to 0.945; p = 0.0002). The estimate, confidence interval and weight of every study are detailed in Table 2, and the same estimates are detailed in Figure 3, which groups the studies by effect source so that the two halves of the literature can be compared directly; study-level estimates ranged from −0.418 to 2.823. Only one study produced a point estimate below zero[49]; that study contributed twelve controls, was drawn from an investigation of polycystic kidney disease rather than designed to characterise essential hypertension, and has the two tightest coefficients of variation in the dataset, so it is weak evidence of a null just as the studies at the other extreme are weak evidence of a large effect. Five studies contributed an effect size of exactly zero by the tier 3 convention, reflecting results their authors reported as non-significant or as a bare direction.

Heterogeneity was substantial and is the dominant feature of this evidence base. The between-study variance was 0.3844 (95% CI 0.2103 to 0.9775), corresponding to a between-study standard deviation of 0.620 (95% CI 0.4586 to 0.9887); the proportion of total variation attributable to heterogeneity was 81.4% (95% CI 73.2 to 87.1), and Cochran Q was 123.83 on 23 degrees of freedom (p < 0.0001). The 95% prediction interval ran from −0.673 to 1.957 and therefore includes zero. This is worth stating plainly: the pooled figure is an average across genuinely dispersed studies, and an individual future study conducted in a new setting could find no difference at all.

Two features of the weighting deserve explicit statement because they are not obvious from the forest plot. First, the five tier 3 studies together carry 20.89% of the total weight, and each carries a variance derived from its group sizes alone. Their contribution to the precision of the pooled estimate is therefore not earned by any published effect size, and the effect is measurable: removing them raises the estimate to 0.812 but widens the confidence interval from 0.605 units (0.340 to 0.945) to 0.688 units (0.468 to 1.156). A specification that drops five studies and produces a wider interval is the signature of precision that was assumed rather than observed, and the primary interval should be read with that in mind. Second, the three largest studies, contributing 404, 364 and 236 participants, together account for 1,004 of the 2,201 participants, which is 45.6%, but receive only 14.79% of the weight. That is the arithmetic of a random-

effects model with a between-study variance of 0.3844 rather than an error, but it has an interpretive consequence: those three studies give 0.524, 0.206 and 0.287, and the fixed-effect estimate of 0.493 sits far closer to them than the random-effects estimate does. More generally, the weights span only 2.55% to 4.97%, a range of 1.95-fold, while total sample sizes span 19 to 404, a range of 21.3-fold: a study with twenty-one times the participants receives less than twice the weight. With a between-study variance of this size the analysis is close to one study one vote, and since twenty-one of the twenty-four studies enrolled fewer than one hundred participants the pooled estimate is in effect an average of small studies.

Two further descriptive features of the distribution belong beside the pooled figure. The median study-level effect is 0.537 and the arithmetic mean of the twenty-four estimates is 0.682, so the pooled value of 0.642 sits above the typical study, pulled up by a small number of large positive outliers, principally the two studies at 2.823 and 2.305; fourteen of the twenty-four studies lie at or below the pooled estimate. And the four studies published since 2020 give, in descending order, 0.524, 0.511, 0.000 and −0.418, which is not obviously the same distribution as the pool as a whole.

Table 2. Study-level and pooled standardised mean differences. Positive values indicate higher circulating ADMA in hypertensive participants. Weights are from the random-effects model.

Study (country)	Source	Hedges g	95% CI	Weight %
Surdacki 1999 (Poland)	Reported	1.296	0.475 to 2.117	3.51
Holm 2002 (Norway)	Tier 3	0.000	−0.502 to 0.502	4.36
Paiva 2002 (Finland)	Reported	1.290	0.677 to 1.903	4.07
Kielstein 2003 (Germany)	Reported	0.708	0.123 to 1.293	4.15
Schlaich 2004 (Australia)	Tier 3	0.000	−0.759 to 0.759	3.68
Curgunlu 2005 (Turkey)	Reported	2.823	2.141 to 3.504	3.89
Perticone 2005 (Italy)	Tier 2	0.775	−0.010 to 1.559	3.61
Tsuda 2005 (Japan)	Tier 3	0.000	−0.459 to 0.459	4.47
Zhang 2005 (China)	Tier 2	0.681	0.158 to 1.203	4.31
Xie 2006 (China)	Tier 2	0.539	−0.005 to 1.082	4.26
Atamer 2008 (Turkey)	Tier 3	0.000	−0.463 to 0.463	4.46
Wang D 2009 (Denmark)	Reported	2.305	1.089 to 3.522	2.55
Perticone 2010 (Italy)	Tier 2	1.021	0.503 to 1.540	4.32
Sonmez 2010 (Turkey)	Tier 1	0.535	0.020 to 1.051	4.33
Wang 2011 (China)	Reported	0.555	0.087 to 1.022	4.45
Karadurmus 2012 (Turkey)	Reported	1.685	1.191 to 2.179	4.39
Gonenc 2013 (Turkey)	Tier 2	0.414	−0.116 to 0.945	4.29
Vasilev 2013 (Bulgaria)	Reported	0.643	−0.029 to 1.315	3.91
Xia 2015 (China)	Tier 2	0.206	0.000 to 0.412	4.97
Gkaliagkousi 2018 (Greece)	Reported	0.287	0.007 to 0.566	4.85
Gamil 2020 (Sudan)	Reported	0.524	0.318 to 0.731	4.97
Charkiewicz 2021 (Poland)	Tier 3	0.000	−0.669 to 0.669	3.92
Ekinci 2021 (Turkey)	Reported	−0.418	−1.142 to 0.305	3.77
Ni 2022 (China)	Reported	0.511	0.071 to 0.951	4.52
Pooled (random effects)	24 studies	0.642	0.340 to 0.945	100

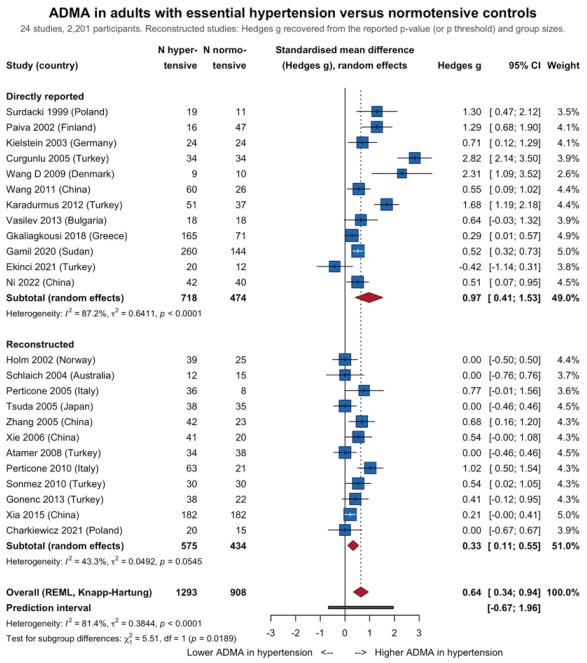

Figure 3. Forest plot of the random-effects meta-analysis of circulating ADMA in essential hypertension versus normotensive controls, grouped by effect source and ordered by year of publication. Squares are study-level Hedges g scaled by weight, horizontal lines are 95% confidence intervals, and the diamond is the pooled random-effects estimate.

3.5. Absolute concentrations and the choice of scale

The standardised scale is necessary for pooling but conceals two things a reader needs. The published means and dispersions for the twelve studies that reported them, together with the raw difference, the ratio of group means and the within-group coefficient of variation, are detailed in Table 3.

The first observation is clinical. Four studies report concentrations that fall within the accepted plasma range of roughly 0.4 to 1.0 micromoles per litre and are free of the anomalies flagged at extraction: the Sudanese case-control study (0.81 against 0.72), the Greek drug-naive cohort (0.98 against 0.89), the Chinese cohort with the mechanistic arm (0.84 against 0.72) and the Bulgarian comparison (0.476 against 0.433). Their raw differences are 0.09, 0.09, 0.12 and 0.043 micromoles per litre, clustering near 0.1. The consistency of that figure across four independent populations, three continents and three assay platforms is a stronger argument for the reality of the association than the pooled standardised estimate, and it is the number a clinician can use.

The second observation is methodological. The within-group coefficient of variation ranges from 9.0% to 78.7% across these twelve studies, a spread of almost ninefold in the dispersion of the same analyte. Because the standardised difference divides by the pooled within-group standard deviation, a study whose assay produced a tight dispersion is rewarded with a large standardised effect irrespective of the size of the biological difference, and the consequence is a reordering that the standardised scale hides. On the ratio of means the largest separation belongs to the Turkish cohort of newly diagnosed young men at 2.64, then the Polish male cohort at 2.18, the Danish microvessel study at 1.95 and the Turkish white-coat comparison at 1.49. On the standardised scale the order is different: the Turkish white-coat comparison leads at 2.823, then the Danish study at 2.305, then the newly diagnosed cohort at 1.685, then the Polish cohort at 1.296. The study identified below as the most influential in the analysis is fourth by ratio of means and first by standardised difference, and the reason is a coefficient of variation of 9.0% in its hypertensive arm, the tightest in the dataset. No pooled ratio-of-means estimate was computed; the per-study ratios in Table 3 are descriptive arithmetic on the published means and are offered so that the reader can see how far the two scales agree.

Three studies report absolute concentrations four to eight times the modern reference range: 2.40 against 1.10, 3.53 against 2.77 and 4.24 against 2.84 micromoles per litre, all measured by chromatographic methods of their period. A purely multiplicative calibration error cancels in a standardised difference, so on that account these three are harmless. They are not equivalent to one another on the dispersion account, however: their hypertensive-arm coefficients of variation are 45.8%, 31.9% and 9.0%, and the third is the extreme value of the entire dataset. All three are examined individually in the sensitivity analysis rather than only the first.

Table 3. Published concentrations, raw differences, ratios of group means and within-group coefficients of variation for the twelve studies reporting means and dispersions. These are descriptive; no pooled estimate was computed on the ratio scale.

Study	Unit as published	Hypertensive mean (SD)	Normotensive mean (SD)	Raw difference	Ratio of means	CV % HT	CV % NT	Hedges g
Surdacki 1999	umol/L	2.40 (1.10)	1.10 (0.70)	1.30	2.18	45.8	63.6	1.296
Paiva 2002	umol/L	0.59 (0.13)	0.43 (0.12)	0.16	1.37	22.0	27.9	1.290
Kielstein 2003	umol/L	3.53 (1.13)	2.77 (0.98)	0.76	1.27	31.9	35.4	0.708
Curgunlu 2005	umol/L	4.24 (0.38)	2.84 (0.58)	1.40	1.49	9.0	20.4	2.823
Wang D 2009	nmol/L	766 (217)	393 (57)	373	1.95	28.3	14.5	2.305
Wang 2011	umol/L	0.0280 (0.0119)	0.0220 (0.0074)	0.0060	1.27	42.3	33.7	0.555
Karadurmus 2012	umol/L	0.837 (0.340)	0.318 (0.250)	0.519	2.64	40.6	78.7	1.685
Vasilev 2013	umol/L	0.476 (0.075)	0.433 (0.054)	0.043	1.10	15.8	12.5	0.643
Gkaliagkousi 2018	umol/L	0.98 (0.31)	0.89 (0.32)	0.09	1.10	31.6	36.0	0.287
Gamil 2020	umol/L	0.81 (0.16)	0.72 (0.19)	0.09	1.13	19.8	26.4	0.524
Ekinci 2021	umol/L	0.39 (0.05)	0.41 (0.04)	−0.02	0.95	12.8	9.8	−0.418
Ni 2022	umol/L	0.84 (0.26)	0.72 (0.20)	0.12	1.17	31.0	27.8	0.511

CV, coefficient of variation (standard deviation divided by the mean). HT, hypertensive; NT, normotensive.

3.6. Sources of heterogeneity

The single largest moderator was not clinical but methodological. Restricted to the twelve studies whose numerical results were directly readable, the estimate was g = 0.972 (95% CI 0.412 to 1.532) with heterogeneity of 87.2%. The twelve studies whose effect sizes were recovered from published test statistics gave g = 0.330 (95% CI 0.109 to 0.551) with heterogeneity of 43.3%. The difference between the two sets was significant (p = 0.019). This gap is the signature of reporting bias operating at the level of data accessibility: the studies whose numbers are easiest to obtain are the studies with the largest effects. One qualification belongs immediately beside it: five of the twelve recovered studies are pinned to exactly zero by the tier 3 convention, and a set containing five constants cannot be heterogeneous, so the lower heterogeneity of the recovered subgroup is partly an artefact of the convention rather than a property of those studies. The interaction was not recomputed within the tier 1 and tier 2 studies alone.

Two moderators admit a biological reading, and one of them requires an immediate caution. Untreated or drug-naive cohorts separated more strongly than mixed or treated cohorts (g = 0.898 versus 0.364; p = 0.040), but the five tier 3 studies are not distributed evenly between those strata: four of the five fall in the mixed or treated stratum and only one in the untreated stratum. Each stratum contains twelve studies, so a third of the treated stratum is pinned at exactly zero against a twelfth of the untreated stratum, and the convention therefore deflates one arm of the comparison more than the other. Part of this contrast is consequently a property of the recovery rather than of the biology. The contrast was not recomputed with the tier 3 studies excluded, so the size of that part is unknown, and the pharmacological reading offered in the Discussion should be weighed accordingly. Studies measuring ADMA in plasma also separated more strongly than those using serum (g = 0.824 versus 0.352; p = 0.045). Publication era showed a similar split (0.846 for 2012 or earlier versus 0.331 for 2013 or later; p = 0.019), but this is largely collinear with effect source and should not be read as a temporal trend in the biology. Assay platform (p = 0.524), study size (p = 0.068) and region (p = 0.826) did not separate the studies. All seven subgroup analyses, with the number of studies and the number of participants at each level, are detailed in Table 4.

Table 4. Subgroup analyses. The p value for interaction is the between-groups Q test.

Moderator	Level	k	Participants	Hedges g	95% CI	I^2 %	p interaction
Effect source	Directly reported	12	1192	0.972	0.412 to 1.532	87.2	0.019
	Reconstructed	12	1009	0.330	0.109 to 0.551	43.3	
Treatment status	Untreated or drug naive	12	1235	0.898	0.409 to 1.387	88.4	0.040
	Mixed or treated	12	966	0.364	0.066 to 0.662	57.3	
Sample matrix	Plasma	16	1436	0.824	0.397 to 1.251	86.3	0.045
	Serum	8	765	0.352	0.062 to 0.642	43.4	
Publication era	2012 or earlier	16	952	0.846	0.416 to 1.275	84.3	0.019
	2013 or later	8	1249	0.331	0.128 to 0.534	39.0	
Study size	Total n < 100	21	1197	0.699	0.349 to 1.048	81.8	0.068
	Total n >= 100	3	1004	0.343	−0.083 to 0.770	58.5	
Assay platform	Chromatographic	17	1807	0.704	0.314 to 1.094	82.8	0.524
	Immunoassay	7	394	0.509	−0.089 to 1.108	79.9	
Region	Europe or Australia	11	686	0.672	0.249 to 1.095	69.9	0.826
	Asia or Africa	13	1515	0.608	0.128 to 1.088	86.7	

The plasma-versus-serum result requires a caution that the subgroup table cannot carry. Sample matrix and assay platform are strongly confounded in this literature, as detailed in Table 5: five of the eight serum studies used an immunoassay against two of the sixteen plasma studies, a share of 62.5% against 12.5%. With twenty-four studies distributed in this way the two variables cannot be separated, and the significant matrix contrast and the null platform contrast are equally consistent with a platform effect that the matrix variable happens to track more efficiently. The defensible statement is that serum studies gave a smaller estimate than plasma studies and were also disproportionately immunoassay studies, and that the available literature does not permit the two explanations to be distinguished.

Table 5. Cross-tabulation of sample matrix against assay platform across the twenty-four included studies.

Sample matrix	Chromatographic (HPLC or LC-MS)	Immunoassay (ELISA or EIA)	Total	Immunoassay share
Plasma	14	2	16	12.5%
Serum	3	5	8	62.5%
Total	17	7	24	29.2%

Meta-regression confirmed the same ordering. Effect source was the only moderator that reached significance, explaining 18.8% of between-study variance (coefficient −0.5995, p = 0.035). Publication year explained 6.1% and did not reach significance (p = 0.144), and its coefficient fell further in a joint model with sample size (p = 0.189). Assay platform and log transformed sample size explained none of the variance. This matters for interpretation: in an analysis restricted to directly reported data the apparent decline of effect size with calendar year is far steeper, and it would have been easy to present that gradient as evidence of improving assay standardisation over time. Once the paywalled studies are recovered the gradient largely disappears, and the earlier era effect is revealed as an artefact of which studies had extractable numbers rather than of when they were performed. The coefficient, standard error, p-value, explained variance and residual between-study variance for every model fitted are detailed in Table 6. No joint model combining effect source with treatment status was fitted, so the treatment-status result is unadjusted and should be read as such; the two variables are only mildly confounded, with seven of the twelve untreated cohorts recovered against five of the twelve mixed or treated cohorts, but that imbalance is not zero and the univariable result cannot exclude it.

Table 6. Mixed-effects meta-regression with restricted maximum likelihood estimation.

Model (single moderator unless stated)	Coefficient	SE	p	R^2 %	Residual tau^2
Effect source (reconstructed vs reported)	−0.5995	0.2675	0.035	18.8	0.3121
Publication year	−0.0324	0.0214	0.144	6.1	0.3612
Assay platform (immunoassay vs chromatographic)	−0.1956	0.3272	0.556	0	0.4071
log (total sample size)	−0.1186	0.2016	0.562	0	0.4040
Year + log(n) joint model: year term	−0.0327	0.0241	0.189	0	0.3860

3.7. Sensitivity analyses

The pooled effect proved robust. Across all thirty-nine pre-specified specifications the estimate ranged from 0.493 to 0.972 and remained statistically significant in every one. The complete leave-one-out series identified a single influential study: removing the Turkish white-coat comparison[32], which reported the largest individual effect and the tightest dispersion, lowered the pooled estimate to 0.538 and reduced heterogeneity from 81.4% to 71.8%, the only omission that materially altered either. The other two studies reporting concentrations far above the modern reference range were less influential: removing the Polish male cohort[27] gave 0.619 and removing the elderly German cohort[30] gave 0.641. Removing the two studies flagged at extraction, one for an implausibly low control mean[42] and one for an internal inconsistency between its abstract and its results section[41], together gave 0.595. Removing the possible cohort overlap gave 0.639. Restricting to established essential hypertension, which removes the borderline-hypertension cohort and the cohort containing prehypertensive participants, gave 0.620.

Three specifications interrogate the recovery procedure itself. Reading every tier 2 threshold at half the stated p-value, a more generous convention that yields larger effects, gave 0.670; reading them at twice the stated p-value, a stricter convention, gave 0.635. The recovery is therefore insensitive to how thresholds are interpreted in aggregate, and the boundary convention used in the primary analysis sits

between the two, moving the pooled estimate by less than 0.04 in either direction. That aggregate stability should not obscure the cost in individual studies: the largest recovered study, a Chinese cohort of 182 against 182 that reported a significant elevation at a threshold of p below 0.05, is entered at 0.206 with a p-value of 0.050, so a result its authors described as significant becomes exactly non-significant, and that study carries the joint-largest weight in the analysis at 4.97%. Excluding the tier 3 recoveries raised the estimate to 0.812, confirming that those studies pull the estimate down rather than up and that their inclusion is conservative for the location of the estimate. Changing the between-study variance estimator or removing the Knapp-Hartung adjustment left the point estimate essentially unchanged and narrowed the interval, as expected. The most informative of the thirty-nine specifications are detailed in Table 7.

Table 7. Selected sensitivity analyses. The complete leave-one-out series is summarised by its most influential members. All thirty-nine specifications remained statistically significant.

Specification	k	Hedges g	95% CI	I^2 %
Primary analysis	24	0.642	0.340 to 0.945	81.4
Omitting Curgunlu 2005 (most influential)	23	0.538	0.302 to 0.775	71.8
Omitting Karadurmus 2012 (flagged control value)	23	0.591	0.292 to 0.890	78.1
Omitting Wang D 2009 (smallest study)	23	0.598	0.308 to 0.887	80.9
Omitting Ekinci 2021 (only negative estimate)	23	0.682	0.381 to 0.983	81.3
Excluding both flagged studies	22	0.595	0.280 to 0.910	79.1
Excluding possible Perticone cohort overlap	23	0.639	0.323 to 0.955	82.2
Established essential hypertension only	22	0.620	0.292 to 0.947	82.1
Untreated or drug-naive cohorts only	12	0.898	0.409 to 1.387	88.4
Chromatographic assays only	17	0.704	0.314 to 1.094	82.8
Directly reported data only	12	0.972	0.412 to 1.532	87.2
Reconstructed data only	12	0.330	0.109 to 0.551	43.3
Excluding Tier 3 null reconstructions	19	0.812	0.468 to 1.156	82.9
Tier 2 thresholds read at half the stated p	24	0.670	0.368 to 0.973	81.5
Tier 2 thresholds read at twice the stated p	24	0.635	0.334 to 0.937	81.5
DerSimonian-Laird estimator	24	0.629	0.404 to 0.854	81.4
Paule-Mandel estimator	24	0.645	0.342 to 0.949	81.4
Knapp-Hartung adjustment removed	24	0.642	0.368 to 0.917	81.4
Fixed-effect (common) model	24	0.493	0.403 to 0.582	81.4

3.8. Small-study effects and publication bias

Small-study effects were present. Begg rank correlation was significant (z = 2.183, p = 0.029) and Egger regression was borderline (t = 1.844, p = 0.079). Trim and fill imputed four missing studies and produced a bias-adjusted estimate of g = 0.407 (95% CI 0.031 to 0.783), which continues to exclude the null. The contour-enhanced funnel plot and the trim-and-fill display are detailed in Figure 4, and the statistic, p-value and bias-adjusted estimate for each test are detailed in Table 8.

One caveat applies to the asymmetry tests and is not usually relevant in a conventional meta-analysis. For the twelve recovered studies the effect size is derived from a published p-value and the two group sizes, so its standard error is a function of those same group sizes; effect and precision are linked by construction in a way they are not for a study that measured a mean and a standard deviation. Funnel-based tests assume that the plotted precision is an independent estimate, and part of the observed asymmetry may therefore reflect the geometry the recovery imposes rather than selective publication. Egger and Begg tests restricted to the twelve directly reported studies were not computed, so this cannot be quantified here; it should be regarded as an open question and a limitation of the method rather than as a reason to discount the finding, since the direction of the asymmetry is the same in both halves of the funnel plot. A second caution runs the other way. The mean effect among the five largest studies is 0.651 and among the five smallest is 0.637, which is almost identical and gives no hint of a size gradient at the extremes, so the asymmetry the rank test detects must arise in the middle of the distribution rather than in the tails. The three largest studies quoted below are the three largest by enrolment, but the fourth largest reports 1.685, and any reading of the funnel plot should acknowledge that the size-effect relationship is not monotonic.

The recovery procedure is what allows this section to reach a conclusion at all. In an analysis restricted to the twelve studies with directly reported numbers, trim and fill also imputed four studies but drove the adjusted estimate to 0.50 with an interval spanning zero, which would have left the review unable to state whether ADMA differs between the groups. With the previously unreadable studies recovered, the adjusted estimate remains positive. The honest summary is therefore that the association is real but modest: the bias-adjusted 0.407, the deliberately conservative recovery-only 0.330 and the primary 0.642 bracket the plausible range, and the three largest and best-reported studies, contributing 404[47], 364[45] and 236[46] participants, sit between 0.206 and 0.524.

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Table 8. Formal tests for small-study effects and publication bias.

Test	Statistic	p	Adjusted estimate	95% CI	Studies imputed
Egger regression	t = 1.844	0.079	not applicable	not applicable	not applicable
Begg rank correlation	z = 2.183	0.029	not applicable	not applicable	not applicable
Trim and fill (random effects)	not applicable	not applicable	0.407	0.031 to 0.783	4

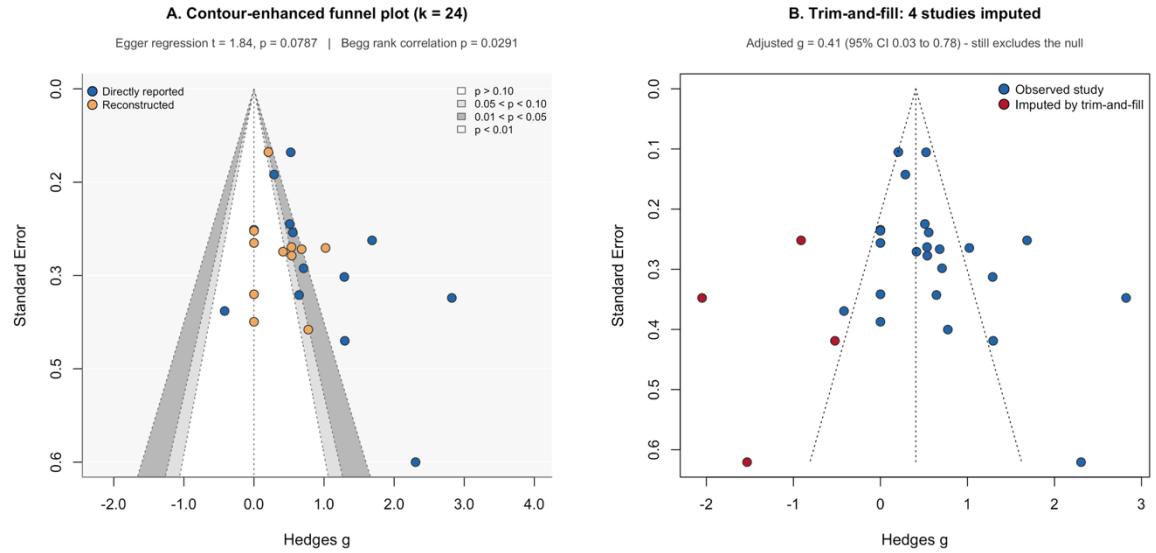

Figure 4. Small-study effects. (A) Contour-enhanced funnel plot with points coloured by effect source, showing the Egger and Begg test results. The recovered studies, in orange, sit almost entirely in the lower-left region of the distribution, which is the visual form of the central finding of this review: the studies whose numerical results are hardest to obtain are also the studies with the smallest effects. (B) Trim-and-fill analysis: four imputed studies shift the pooled estimate to 0.407 (95% CI 0.031 to 0.783), which still excludes the null.

3.9. Certainty of the evidence

Certainty in the pooled estimate was assessed post hoc across the standard domains, and the judgement and reason for each domain are detailed in Table 9. The body of evidence begins low because every contributing study is observational, and is downgraded once for risk of bias, once for inconsistency, once for indirectness and once for publication bias, giving an overall rating of very low. The indirectness downgrade follows from the case-definition departures enumerated above: a population that mixes borderline hypertension, prehypertension, an exclusively elderly cohort, a comparator arm drawn from a study of another disease and five male-only cohorts is not uniformly the population the review question names, and it would be inconsistent to enumerate those departures in the results and then grade the body of evidence as though they were absent. The direction of the association is consistent across every specification tested, but its magnitude should be regarded as poorly established, and this rating rather than the point estimate should govern how the finding is used.

Table 9. Certainty of the evidence for the difference in circulating ADMA between adults with essential hypertension and normotensive controls.

Domain	Judgement	Reason
Study design	Starts low	All twenty-four contributing studies are observational case-control or cross-sectional comparisons.
Risk of bias	Downgrade one level	No study was rated at low risk of bias overall; nine were high risk and fifteen raised some concerns. Twelve studies were appraised from an abstract alone.
Inconsistency	Downgrade one level	I^2 = 81.4% (95% CI 73.2 to 87.1) and the 95% prediction interval (−0.673 to 1.957) includes zero.
Indirectness	Downgrade one level	The comparator and the outcome match the review question but the population does not uniformly: the pool contains borderline hypertension, an arm including prehypertensive participants, an exclusively elderly cohort, a comparator arm drawn from a study of polycystic kidney disease and five male-only cohorts.
Imprecision	No downgrade	The pooled interval (0.340 to 0.945) excludes the null and 2,201 participants exceed the optimal information size for a moderate standardised difference.
Publication bias	Downgrade one level	Begg rank correlation p = 0.029, Egger p = 0.079, and trim and fill imputes four studies and lowers the estimate to 0.407.
Overall certainty	Very low	Four downgrades from a base that already starts low. The direction of the association is consistent across every specification tested, but its magnitude should be regarded as poorly established.

4. Discussion

4.1. Principal findings

This is the first quantitative synthesis of circulating ADMA in essential hypertension compared with normotension. Across twenty-four studies and 2,201 participants, ADMA was higher in hypertension by 0.642 standardised units, an effect of moderate size by conventional benchmarks and, among the four studies reporting concentrations within the accepted range, a raw difference of roughly 0.1 micromoles per litre. Four qualifications belong beside that number rather than beneath it. Heterogeneity was 81.4%; the 95% prediction interval includes zero; small-study effects were

e-ISSN: 2988-3237
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demonstrable, with the bias-adjusted estimate falling to 0.407; and the certainty of the evidence is very low. Taken together these place the plausible magnitude of the association at roughly a third to a half of a standard deviation.

The second principal finding is methodological but has direct substantive consequences. Effect source was the strongest moderator identified, stronger than treatment status, sample matrix, assay platform, study size or region. Studies whose numbers could be read directly gave an estimate three times larger than studies whose effect sizes had to be recovered from published test statistics. Since the tier 2 convention is a genuine lower bound and can only understate effects, the gap cannot be an artefact of the procedure in the direction that would explain it away. The most economical explanation is that accessibility of numerical results is itself correlated with the size of those results.

4.2. Comparison with the existing literature

No previous meta-analysis has addressed this contrast, so direct comparison is not possible. The estimate can, however, be placed against syntheses of ADMA in adjacent conditions, which have generally reported associations of comparable or larger magnitude in coronary artery disease, heart failure, chronic kidney disease and preeclampsia. That comparison is necessarily loose, because several of those syntheses pooled odds ratios or hazard ratios rather than standardised mean differences and are not strictly commensurable with the present estimate. That essential hypertension should sit at the lower end of that range is biologically unsurprising: it is the least advanced and least tissue-destructive of those states, and the populations studied are the least selected. Individual observations in the recent literature are consistent with a real but modest signal. Higher ADMA has been associated with reduced myocardial mechano-energetic efficiency specifically in hypertensive subjects[15], with sarcopenia in community-dwelling older women[51], with angiogenic impairment in type 2 diabetes and prediabetes[52], and with adverse profiles in cyanotic congenital heart disease[53] and in advanced pulmonary arterial hypertension[54]. The same direction is seen across a range of vascular states: prospectively in cerebrovascular disease[55], in the collateral circulation of acute ischaemic stroke[56], in the peripheral microangiopathy of systemic sclerosis[57], in sickle cell disease[58], and in HIV-associated preeclampsia, where the enzyme that clears ADMA is itself implicated[59] and polymorphisms in that enzyme track with maternal concentrations[60]. Against these, the finding that vascular dysfunction in chronic kidney disease tracks with symmetric rather than asymmetric dimethylarginine[20], the finding that the symmetric isomer rather than ADMA predicted occult atrial fibrillation after ischaemic stroke[61], and the observation that L-homoarginine rather than ADMA predicted mortality in one large cohort[62], caution against treating ADMA as the single informative member of the methylarginine family.

4.3. Mechanistic interpretation

A modest group difference is what the underlying biology would predict. ADMA is a competitive inhibitor, so its effect on nitric oxide synthesis depends on the prevailing ratio of substrate to inhibitor rather than on inhibitor concentration alone, and the physiological range of ADMA is narrow. Clearance depends on DDAH1 and on renal excretion[11], and renal function underpins the pathway more broadly in both mice and humans[13], so any difference between hypertensive and normotensive groups will be partly a function of how closely the groups are matched for glomerular filtration. That ADMA can enable depolarising spikes and vasospasm in resistance arteries supplies a plausible route from small concentration differences to haemodynamically meaningful effects[14], and mechanical force has been shown to regulate DDAH1-mediated ADMA hydrolysis[12], which raises the possibility that the relationship between pressure and ADMA is bidirectional rather than causal in one direction only. The pathway is one of several converging on endothelial nitric oxide: targeting the cytokine-like protein FAM3D lowers blood pressure in experimental hypertension[63], and circulating trimethylamine N-oxide tracks with vascular function in hypertensive patients[64], so ADMA is best read as one contributor among several rather than as the pathway itself.

The treatment-status subgroup is consistent with that reading but does not establish it, and two explanations deserve equal weight. The first is pharmacological: if antihypertensive therapy lowers ADMA, as one included study demonstrated directly for enalapril and losartan[35], as post-hoc analysis of a randomised trial has shown for metformin[65] and as trial evidence for renin-angiotensin blockade in other populations suggests[66], then the case-control gap should narrow in treated populations exactly as observed. The second is selection: treated patients are further from diagnosis, are by definition under management, and may have better controlled and therefore milder disease at the time of sampling, which would produce the same subgroup result through a different mechanism. Cross-sectional data cannot distinguish these, no joint model adjusting for effect source was fitted, and the subgroup difference should therefore be treated as hypothesis-generating. Recent randomised evidence in diabetic hypertension has continued to explore whether particular agents confer vascular benefit beyond pressure lowering[67], and non-pharmacological approaches that raise nitric oxide availability, including citrulline supplementation[68], dietary sodium restriction[69] and structured lifestyle modification[70], act on the same axis.

4.4. What the recovery procedure reveals about this literature

The most uncomfortable finding of this review is not about ADMA at all. Twelve of the twenty-four eligible studies could not be entered into a conventional meta-analysis because their group-level numbers are not publicly readable, and those twelve are systematically different from the twelve that are. Had the conventional approach been followed, this review would have reported an estimate of 0.972 with heterogeneity of 87.2%, and trim-and-fill adjustment would then have collapsed that estimate to a confidence interval containing zero.

4.5. Clinical implications

The clinical message is deliberately restrictive. A raw difference of roughly 0.1 micromoles per litre, on group means of 0.7 to 1.0, corresponds to substantial overlap between the hypertensive and normotensive distributions, and the standardised estimate of about half a standard deviation, plausibly as little as 0.3 to 0.4 after bias adjustment, says the same thing in different units. ADMA therefore separates groups on average but cannot classify individuals, and nothing in these data supports measuring ADMA to diagnose hypertension, to grade its severity in an individual patient, or to guide treatment choice. With certainty rated very low, this conclusion should be stated as firmly as the positive finding, because biomarker literatures characteristically drift from a modest group-level association towards implied individual-level utility that the effect size never supported.

Where the finding does carry weight is mechanistic and population-level. It supports the nitric oxide pathway as a genuine participant in human essential hypertension rather than an inference from animal models, and it identifies untreated, newly diagnosed patients as the population in

e-ISSN: 2988-3237
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whom that participation is most visible. That recommendation carries its own caveat: the untreated subgroup is also where heterogeneity is highest, at 88.4% against 57.3% in the treated and mixed cohorts, and seven of its twelve members entered through recovery rather than measurement, so it is simultaneously the subgroup with the largest estimate and the one with the least directly observed data. For nephrology and hypertension services in particular, the dependence of ADMA clearance on renal function means that any future clinical use would have to be interpreted against glomerular filtration rather than in isolation, and that hypertensive patients with declining renal function are the group in whom ADMA is least likely to behave as a specific marker of vascular disease. It is also worth noting what ADMA would have to compete against: models built on the resting electrocardiogram already predict incident hypertension without any assay at all[71], so a blood biomarker of this effect size faces a demanding comparator before it could earn a place in practice.

One clinically important question is deliberately outside the scope of this review and should be named. This synthesis answers a case-control question: whether hypertensive groups differ from normotensive groups. The more actionable question for a hypertension service is whether ADMA tracks severity, control or target-organ damage within hypertensive patients, and at least four included studies report data of that kind, relating ADMA to hypertension grade[41], to dipping status[43], to carotid intima-media thickness and plaque score[45] and to aortic augmentation index[46]; outside this pool, ADMA has also been related to circadian blood-pressure variability[72]. Those within-disease gradients were not extracted or synthesised here, and a reader should not infer from a positive case-control result that ADMA rises with severity. That is a separate review, and the studies to support it exist.

4.6. Strengths and limitations

The principal strength of this review is that it recovers and quantifies a body of evidence that conventional methods would have discarded, and then measures the consequence of that discarding. Thirty-nine pre-specified sensitivity specifications, including two that interrogate the recovery convention directly, support the robustness of the result. Every included record was verified against its primary index entry, and one duplicate cohort and one internally implausible report were identified and excluded that a search relying on titles alone would have retained.

The limitations are substantial and should govern how the estimate is used. Heterogeneity of 81.4% is high, and the prediction interval includes zero. Small-study effects are demonstrable and the bias-adjusted estimate is materially lower than the primary one. No included study was rated at low risk of bias overall, twenty-one of twenty-four enrolled fewer than one hundred participants, and the overall certainty of the evidence is very low. The twelve recovered studies were appraised from their abstracts alone, so their risk-of-bias ratings are less informative than those of the remainder, and two of them, both published in Chinese, were never read in full; their entire contribution rests on an English abstract. The tier 3 convention contributes precision it did not earn, as quantified in the Results. Renal function, the most important single confounder given the clearance route of ADMA, was too inconsistently reported to enter meta-regression; body composition may matter for the same reason, since ADMA concentrations differ between normal-weight and obese patients with chronic kidney disease[73]. This is not a minor residual confounder but a plausible partial explanation of the finding, since hypertensive populations have lower glomerular filtration than normotensive ones by the natural history of the disease, and it is most acute in the exclusively elderly cohort[30], whose removal moved the estimate only from 0.642 to 0.641. Finally, all included studies are cross-sectional or case-control in design, so no causal direction can be inferred: raised ADMA may contribute to hypertension, follow from it, or reflect a shared antecedent such as reduced renal clearance.

5. Conclusion

Circulating asymmetric dimethylarginine is higher in adults with essential hypertension than in normotensive controls, with a pooled Hedges g of 0.642 (95% CI 0.340 to 0.945) across twenty-four studies and 2,201 participants, corresponding to a raw difference of roughly 0.1 micromoles per litre in the studies reporting concentrations within the accepted range. The association is robust to every sensitivity specification tested but is accompanied by substantial heterogeneity, a prediction interval that includes zero, demonstrable small-study effects that reduce the bias-adjusted estimate to 0.407, and an overall certainty rating of very low. The difference is therefore real but modest, and the distributions overlap far too much for ADMA to serve as a diagnostic marker in an individual patient. The finding supports the nitric oxide pathway as a participant in human essential hypertension and identifies untreated, newly diagnosed patients as the population in whom that participation is most evident, while noting that this is also the subgroup resting on the least directly observed data. Separately, the threefold difference between estimates derived from directly readable and from recovered data is a measurable demonstration of accessibility bias in this literature, and argues that group-level summary statistics should be reported in the abstract of every case-control biomarker study.

Acknowledgements

The authors thank the Division of Nephrology and Hypertension, Department of Internal Medicine, Faculty of Medicine, Universitas Andalas and Dr. M. Djamil General Hospital, Padang, for institutional support.

Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Conflict of interest

The authors declare that they have no competing interests.

Ethical considerations

This study is a systematic review and meta-analysis of previously published, de-identified aggregate data. No new data were collected from human participants and no individual patient data were accessed, so ethical approval and patient consent were not applicable.

Data availability

The extracted dataset, the analysis scripts, the complete leave-one-out series, the full search strings and all intermediate result files are available from the corresponding author on reasonable request.

Author contributions

All authors contributed to the conception and design of the review, to the interpretation of the findings, and to drafting and critically revising the manuscript. All authors approved the final version and agree to be accountable for all aspects of the work.

Use of artificial intelligence

None declared. All study selection, data extraction and interpretation were performed by the authors, every included record and reference was verified against its primary source, and the authors reviewed, corrected and

approved the entire manuscript and take full responsibility for its content.

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