HYPERTENSION, TYPE 2 DIABETES, AND CARDIOVASCULAR RISK: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Abstract

Hypertension and type 2 diabetes mellitus (T2DM) are major cardiometabolic risk factors worldwide, yet observational evidence has not always distinguished their independent associations with specific cardiovascular outcome families. To systematically review recent observational studies examining the independent association of hypertension, and separately T2DM, with cardiovascular risk, and to conduct quantitative synthesis only in prespecified subgroups with sufficient methodological comparability. PubMed/MEDLINE, Scopus, and Web of Science were searched in January 2025 for English-language cohort studies published from January 2011 onward. Sixteen cohort studies met PECO eligibility criteria (nine hypertension, seven T2DM). Methodological quality was assessed using the Newcastle-Ottawa Scale. Random-effects meta-analysis was conducted only for prespecified subgroups with at least three sufficiently comparable hazard-based estimates; smaller or non-comparable strata were synthesized narratively. Reporting followed PRISMA 2020 and MOOSE guidance. Stage 1 hypertension was associated with higher broad composite CVD risk (HR = 1.42; 95% CI: 1.24–1.62; I^2 = 81.1%; n = 6). T2DM was associated with higher heart failure risk (HR = 1.57; 95% CI: 1.38–1.78; I^2 = 79.7%; n = 4). Narrative evidence for hypertension-related stroke, cardiovascular mortality, T2DM-related broad CVD, coronary events, and cardiovascular mortality was directionally positive but limited by small study counts and lack of direct quantitative comparability. Recent observational evidence supports an association of stage 1 hypertension with broad composite CVD and of T2DM with heart failure, while evidence for other outcome families remains suggestive rather than definitive. Findings support cautious, exposure-specific

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Gland Surg
VOL-11 NO 1 (2026)
ISSN:2227-684X | E-ISSN:2227-8575

cardiometabolic risk assessment and should not be interpreted as providing equally certain estimates across all cardiovascular domains.

Keywords: *hypertension; type 2 diabetes mellitus; cardiovascular disease; meta-analysis; systematic review; cardiometabolic risk*

1. Introduction

1.1 Global Burden and Clinical Importance

The leading cause of mortality in the world is cardiovascular disease (CVD), with the annual death rate of 17.9 million and almost a quarter of the total world mortality (WHO, 2023a). One point two eight billion adults worldwide are currently estimated to have hypertension, and 537 million adults worldwide are estimated to have lived with diabetes in 2021, the vast majority of which is T2DM and are projected to reach more than 783 million by 2045 (IDF, 2021; WHO, 2023b). The two conditions are both associated with high cardiovascular morbidity, hypertension is the most attributable risk factor to ischemic heart disease and stroke (GBD 2019 Risk Factors Collaborators, 2020), and T2DM is an independent risk factor for coronary artery disease, heart failure, peripheral arterial disease, and cardiovascular death. Even small increases in blood pressure and initial glycemic dysregulation have cardiovascular implications, which are quantifiable, and it is necessary to synthesize their respective contributions to cardiovascular risk systematically and up-to-date.

1.2 Pathophysiological Basis and Epidemiologic Co-occurrence

Hypertension and T2DM both contribute to cardiovascular vulnerability independently but not entirely by similar but somewhat different mechanisms. Persistently high blood pressure fosters endothelial dysfunction, stiffness of the arterial walls, left ventricular hypertrophy and high cardiac afterload (Laurent et al., 2006). The resistance to insulin and persistent hyperglycemia in T2DM disrupts the bioavailability of nitric oxide, facilitates systemic oxidative stress and inflammation, atherosclerosis, and causes metabolic cardiomyopathy, which predisposes the patient to heart failure despite the absence of obstructive coronary artery disease (Haffner et al., 1998; Satt T2DM has an epidemiological co-occurring condition of hypertension diagnosis (40-80%), which is an expression of common etiological factors such as visceral adiposity, activation of the sympathetic nervous system, and dysregulation of the renin-angiotensin-aldosterone system (Ferrannini & Cushman, 2012). Although this occurs co-morbidly, the current review purposefully examines both exposures separately and maintains the biological distinctive signature and clinical endpoint features of each disorder and does not over-pool mechanistically heterogeneous pathways.

1.3 Evidence Gaps and Rationale

Although there is considerable observational literature, this has a number of limitations that limit interpretability. The estimates of the effect differ widely among definitions of exposure, and after the reclassification of stage 1 hypertension to systolic 130-139 mmHg or diastolic 80-89 mmHg, heterogeneous results were obtained across cohorts of different ages, ethnicities, and clinical setting (Carey et al., 2018). Cardiovascular outcome measures used in different studies are not uniform with composite CVD, stroke, heart failure, coronary events and mortality mostly used interchangeably making comparison of different studies difficult. In addition, most of the previous syntheses precede large-scale Scandinavian, Chinese, and UK registry-based cohort studies with better confounder adjustment and countrywide coverage. This propensity to come up with one pooled estimate of heterogeneous exposures is prone to generate clinically misleading composite associations that

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Gland Surg
VOL-11 NO 1 (2026)
ISSN:2227-684X | E-ISSN:2227-8575

conceal subgroup-level variation (Stroup et al., 2000). The current review fills these gaps by using meta-analysis of exposure-specific and outcome-family subgroups using 16 recent peer-reviewed studies.

1.4 Review Objectives

The main research question was as follows: In adults, how hypertension and separately type 2 diabetes mellitus (T2DM) is independently related to incident cardiovascular outcomes in peer-reviewed observational studies published from January 2011 to the January 2025 search date?

The main aim was the critical assessment and quantitative synthesis of this evidence by subgroup meta-analysis in prespecified and analytically coherent strata. Two domains of exposure, hypertension and T2DM, were examined individually and five cardiovascular outcome groups, broad composite CVD, stroke, heart failure, coronary events, and cardiovascular mortality, were considered analytically distinct. This stratification had seven prespecified subgroups that organized the whole synthesis: HTN BroadCVD, HTN Stroke, HTN CVDMortality, T2D HF, T2D BroadCVD, T2D Coronary, and T2D CVDMortality. The eligible research designs included prospective cohort studies, retrospective cohort studies, and registry-based cohort studies; cross-sectional designs were excluded because they could not establish temporality.

Complementary analyses were guided by three secondary objectives, which were to compare the magnitude of pooled effect estimates across outcome family in each exposure domain; to identify and, where feasible, explain the sources of between-study heterogeneity through pre-specified moderator analyses; and to derive clinical and public-health implications of the synthesized evidence. Subgroups that had less than three primary studies in their support were not meta-analyzed and were summarized in a narrative manner.

2. Methods

2.1 Review Design and Reporting Standard

The study was a selective subgroup meta-analysis systematic review that was reported according to the PRISMA 2020 statement (Page et al., 2021), Cochrane Handbook (Higgins et al., 2023), and the MOOSE reporting framework (Stroup et al., 2000). The registration of a formal prospective protocol was not done but the eligibility criteria, their subgroups and their synthesis rules were described in advance prior to the extraction of data, and this is reported openly here.

2.2 Eligibility Criteria

Eligible participants were adults (>=18 years) identified in community-based, national registry, or other similar sources of observational data. The exposure criteria were hypertension (stage 1 or 2 according to the 2017 ACC/AHA guideline or physician-diagnosed) or T2DM (registry codes, clinical diagnosis, or standard criteria: fasting plasma glucose >=7.0 mmol/L or HbA1c >=48 mmol/mol), both of which mandatory required a well-defined comparator. Research studies had to record one or more eligible cardiovascular endpoints that had a full adjusted effect estimate and 95% confidence interval. The predictive ratios of hazards and subdistribution hazards were only potentially poolable when the subgroup could be otherwise regarded as clinically and methodologically coherent; odds ratios and estimates that were not directly comparable to the main hazards based models were stored to be narratively synthesized. The possible designs were prospective, retrospective, and registry-based cohort studies published in the English language since January 2011 up to the January 2025 search

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Gland Surg
VOL-11 NO 1 (2026)
ISSN:2227-684X | E-ISSN:2227-8575

date. The entire eligibility system is outlined in Table 1.

Table 1

Eligibility Criteria for Inclusion and Exclusion of Studies

PECO Dimension	Inclusion Criteria	Exclusion Criteria
Population	Adults >=18 years; community cohorts, national registries, or linked health record platforms	Pediatric-only populations; animal studies
Exposure	Hypertension (stage 1/2, elevated BP, or physician-diagnosed) OR type 2 diabetes (registry code, clinical diagnosis, or standard diagnostic criteria)	Type 1 diabetes only; gestational diabetes; no clearly defined exposure
Comparator	Normotension or lower BP category (HTN); non-diabetic control group (T2DM)	No comparator defined; within-exposure comparisons only
Outcomes	Composite CVD; stroke; heart failure; coronary events (AMI/CHD); cardiovascular mortality	Intermediate/surrogate outcomes only; non-cardiovascular outcomes only
Study Design	Prospective, retrospective, or registry-based cohort; peer-reviewed; adjusted HR/OR/sub-HR with 95% CI	Reviews; editorials; protocols; case reports; cross-sectional; no extractable adjusted estimate
Publication Period	January 2011 - January 2025 search date	After the January 2025 search date
Language	English-language publications	Non-English without available translation

Note. BP = blood pressure; CVD = cardiovascular disease; HTN = hypertension; T2DM = type 2 diabetes mellitus; HR = hazard ratio; OR = odds ratio; CI = confidence interval.

2.3 Search Strategy and Information Sources

PubMed/MEDLINE, Scopus and Web of Science Core Collection were searched on January 2025 to identify studies published between January 2011 and the January 2025 search date. Search strings were used to combine blocks of keywords with hypertension/blood pressure, T2DM, and cardiovascular outcomes with Boolean AND operator and Boolean OR operator respectively. Limiters in the study-design (cohort, prospective, registry) were added. Citation chasing of reference lists of included studies and high-relevance prior systematic reviews was used to supplement electronic retrieval. Table 2 summarizes representative search strings, and any such version that has been submitted to peer review must contain complete reproducible search strings in a supplement.

Table 2

Database Search Strategy and Representative Search Terms

Database	Date	Search String (Illustrative)

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Gland Surg
VOL-11 NO 1 (2026)
ISSN:2227-684X | E-ISSN:2227-8575

PubMed / MEDLINE	Jan 2025	((hypertension[Title/Abstract] OR "blood pressure"[Title/Abstract]) OR ("type 2 diabetes"[Title/Abstract] OR "Diabetes Mellitus, Type 2"[Mesh])) AND ("cardiovascular disease"[Title/Abstract] OR stroke[Title/Abstract] OR "heart failure"[Title/Abstract]) AND (cohort OR registry) AND limited to publications from January 2011 through the January 2025 search date
Scopus	Jan 2025	TITLE-ABS-KEY(hypertension OR "type 2 diabetes") AND TITLE-ABS-KEY("cardiovascular disease" OR stroke OR "heart failure" OR "coronary events") AND TITLE-ABS-KEY(cohort OR registry), limited to publications from January 2011 through the January 2025 search date
Web of Science	Jan 2025	TS=(hypertension OR "type 2 diabetes") AND TS=("cardiovascular disease" OR stroke OR "heart failure") AND TS=(cohort OR registry), limited to publications from January 2011 through the January 2025 search date
Citation chasing	Jan 2025	Reference lists of included studies; high-relevance prior systematic reviews; publisher platforms for DOI verification

Note. Full reproducible search strategies, including MeSH-expanded and platform-specific syntax, should be supplied in a supplement for peer-review submission. Current table shows representative search strings only. Restricted to English-language publications, January 2011 through the January 2025 search date.

2.4 Study Selection, Data Extraction, and Risk-of-Bias Assessment

Records were merged, deduplicated, then screened at title/abstract and full-text levels against predefined PECO criteria; full-text exclusion reasons were recorded systematically. Data extraction used a standardized template capturing study design, sample size, exposure and comparator definitions, follow-up duration, outcome family, effect measure type, adjusted point estimate with 95% CI, and key covariates. Standard errors for meta-analysis were derived as SE = [ln(upper CI) - ln(lower CI)] / 3.92. Methodological quality was appraised using the Newcastle-Ottawa Scale (NOS), with studies classified as low risk (NOS >=7), moderate risk (5-6), or higher risk (<5 stars; Wells et al., 2013).

2.5 Statistical Analysis

The estimation of ratios was all log-transformed before pooling and back-transformed to report. A prespecified subgroups of the sample that were perceived to be adequately similar in the definition of exposure, outcome family, and effect-measure structure were analyzed by the DerSimonian-Laird random-effects model. The pooling was limited to subgroups which contained at least three contributing hazard based estimates; smaller subgroups and strata whose estimates were materially non-comparable were pooled narratively. Between-study heterogeneity was quantified by I^2 and Cochran Q (alpha = 0.10), interpreted as low (<25%), moderate (25-50%), substantial (50-75%), or considerable (>75%). Leave-one-out influence analyses examined robustness of the two primary pooled models. Sensitivity analyses excluded studies with NOS <=6. Funnel plots were generated for the pooled subgroups as qualitative displays only; formal Egger's regression was not applied given

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Gland Surg
VOL-11 NO 1 (2026)
ISSN:2227-684X | E-ISSN:2227-8575

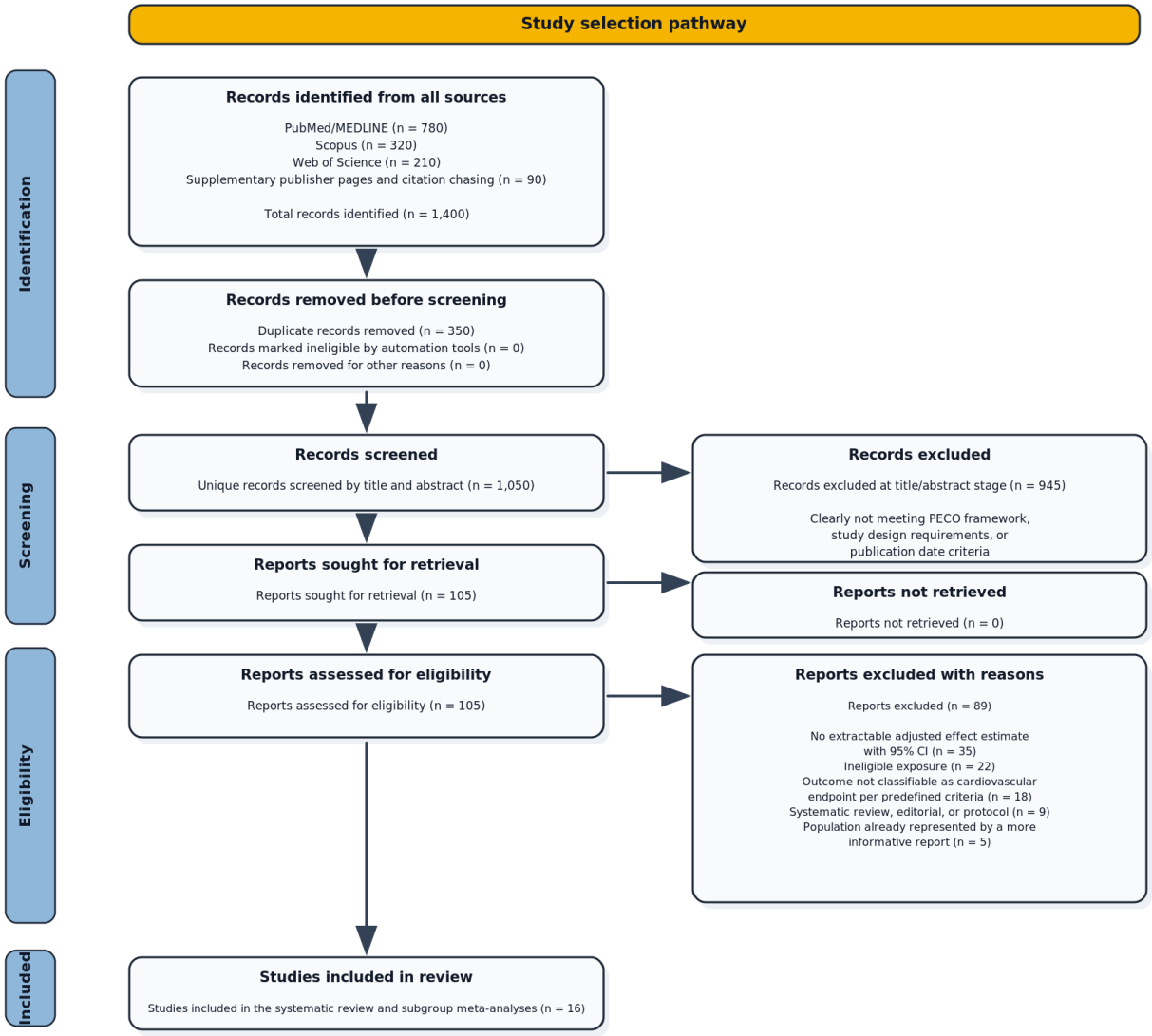
subgroup sizes of n < 10 (Page et al., 2021).

3. Results

3.1 Study Selection

This was followed by database and additional searches that resulted in the identification of 1,400 records (PubMed: 780; Scopus: 320; Web of Science: 210; other: 90). Having eliminated 350 duplicates, 1,050 records were filtered; 945 records were filtered out at title/abstract. Among 105 full-text reports evaluated, 89 were not selected (no adjustable estimate/CI, n = 35; wrong exposure, n = 22; wrong outcome, n = 18; unsuitable design, n = 9; duplicate cohort, n = 5). Sixteen studies qualify all the inclusion criteria and are stored in the systematic review and subgroup meta-analyses.

Figure 1. PRISMA diagram



3.2 Characteristics of Included Studies

The 16 studies comprised nine in the hypertension domain and seven in the T2DM domain, published 2015-2024. Geographically, nine were Asian cohorts (predominantly China and Singapore), four Scandinavian national registries (Sweden and Denmark), two European/Mediterranean cohorts

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Gland Surg
VOL-11 NO 1 (2026)
ISSN:2227-684X | E-ISSN:2227-8575

(England and Greece), and one North American (United States). Sample sizes ranged from 1,403 (Critselis et al., 2019) to 2,605,199 (Tancredi et al., 2019). All nine hypertension studies defined exposure as stage 1 hypertension per the 2017 ACC/AHA classification (follow-up 10-20 years); all seven T2DM studies ascertained exposure via registry codes or clinical criteria (follow-up 5.1-10 years). Detailed characteristics are presented in Table 3.

Table 3

Characteristics of Studies Included in the Systematic Review and Subgroup Meta-Analyses

Author Year	Country/Cohort	Exposure	Comparator	Outcome Family	N Total	Effect (95% CI)
Yano 2018	USA (CARDIA)	Stage 1 HTN	Normal BP	Broad CVD	4,851	HR 1.75 (1.22-2.53)
Qi 2018	China (CMPC)	Stage 1 HTN	BP <120/<80	Broad CVD	21,441	HR 1.78 (1.50-2.11)
Ji 2019	China (N. cohort)	Stage 1 HTN	Normal BP	Broad CVD	97,126	HR 1.25 (1.11-1.40)
Critselis 2019	Greece (ATTICA)	Stage 1 HTN	Normotension	Broad CVD	1,403	HR 1.90 (1.16-3.08)
Liu 2020	China (rural)	Stage 1 HTN	Normal BP	Stroke	20,072	HR 1.53 (1.20-1.95)
Wu 2021	China (Liaoning)	Stage 1 HTN	Normal BP	CVD Mortality	19,374	HR 1.69 (1.20-2.39)
Talaei 2018	Singapore (SCHS)	Stage 1 HTN	Normal BP	CVD Mortality	30,636	HR 0.94 (0.81-1.11)
Gao 2024	China (large cohort)	Stage 1 HTN	Normal BP	Broad CVD	103,651	HR 1.20

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Gland Surg
VOL-11 NO 1 (2026)
ISSN:2227-684X | E-ISSN:2227-8575

						(1.13-1.25)
Kailuan 2023	China (Kailuan)	Stage 1 HTN	Normal BP	Broad CVD	96,268	HR 1.35 (1.19-1.52)
Shah 2015	England (CALIBER)	T2DM	No diabetes	Heart Failure	1,921,260	HR 1.56 (1.45-1.69)
Rawshani 2018	Sweden (NDR)	T2DM	Matched controls	Heart Failure	1,627,044	HR 1.45 (1.34-1.57)
Rosengren 2018	Sweden (NDR)	T2DM	Matched controls	Heart Failure	1,589,809	HR 2.07 (1.73-2.48)
Larsson 2018	Sweden (cohorts)	T2DM	No diabetes	Heart Failure	71,483	HR 1.34 (1.14-1.66)
Gyldenkerne 2023	Denmark (national)	T2DM (new)	Matched general pop.	Broad CVD	530,997	sub-HR 1.91 (1.76-2.07)
Tancredi 2019	Sweden (NDR)	T2DM	Population controls	Coronary events	2,605,199	HR 1.42 (1.41-1.44)
Tancredi 2015	Sweden (NDR)	T2DM	Population controls	CVD Mortality	~435,000	HR 1.14 (1.13-1.15)

Note. Blue shading = Hypertension domain; Red shading = T2DM domain. HR = hazard ratio; sub-HR = subdistribution hazard ratio; NDR = National Diabetes Register; CARDIA = Coronary Artery Risk Development in Young Adults; CMPC = Chinese Multi-Provincial Cohort; CALIBER = ClinicAl research using LInked Bespoke studies and Electronic health Records.

3.3 Risk-of-Bias Assessment

Fifteen studies were classified as low risk of bias (NOS >=7), including the large Scandinavian registry-based studies and most hypertension cohorts; one study (Liu et al., 2020) was rated moderate

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ISSN:2227-684X | E-ISSN:2227-8575

quality (NOS = 6). The most common bias sources were residual confounding by lifestyle factors, heterogeneous blood pressure measurement, and inconsistent cardiovascular outcome ascertainment. Detailed NOS ratings are in Table 4.

Table 4

Risk-of-Bias Assessment of Included Observational Studies (Newcastle-Ottawa Scale)

Study	Domain	Selection (0-4)	Comparability (0-2)	Outcome (0-3)	Total (0-9)	Risk Level
Yano 2018	HTN	3	2	2	7	Low
Qi 2018	HTN	4	2	2	8	Low
Ji 2019	HTN	3	2	2	7	Low
Critselis 2019	HTN	3	2	2	7	Low
Liu 2020	HTN	3	1	2	6	Moderate
Wu 2021	HTN	3	2	2	7	Low
Talaei 2018	HTN	3	2	2	7	Low
Gao 2024	HTN	4	2	3	9	Low
Kailuan 2023	HTN	4	2	2	8	Low
Shah 2015	T2DM	4	2	3	9	Low
Rawshani 2018	T2DM	4	2	3	9	Low
Rosengren 2018	T2DM	4	2	3	9	Low
Larsson 2018	T2DM	3	2	2	7	Low
Gyldenkerne 2023	T2DM	4	2	3	9	Low
Tancredi 2019	T2DM	4	2	3	9	Low
Tancredi 2015	T2DM	4	2	3	9	Low

Note. Total >=7 = Low risk; 5-6 = Moderate risk; <5 = Higher risk.

3.4 Meta-Analysis of Hypertension and Cardiovascular Risk

HTN-Broad CVD Subgroup (Primary Pooled Model)

Six studies contributed: Yano et al. (2018), Qi et al. (2018), Ji et al. (2019), Critselis et al. (2019), Gao et al. (2024), and Kailuan/JAHA (2023). The DerSimonian-Laird pooled HR was **1.42 (95% CI: 1.24-1.62, p < 0.001)**, representing a statistically significant 42% elevation in broad CVD risk with stage 1 hypertension. Between-study heterogeneity was substantial ($I^2 = 81.1\%$, $Q = 26.41$, $df = 5$, $p < 0.001$, $\tau^2 = 0.0189$). Individual estimates ranged from HR 1.20 (Gao et al., 2024) to HR 1.90 (Critselis et al., 2019). The forest plot is presented in Figure 2.

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Gland Surg
VOL-11 NO 1 (2026)
ISSN:2227-684X | E-ISSN:2227-8575

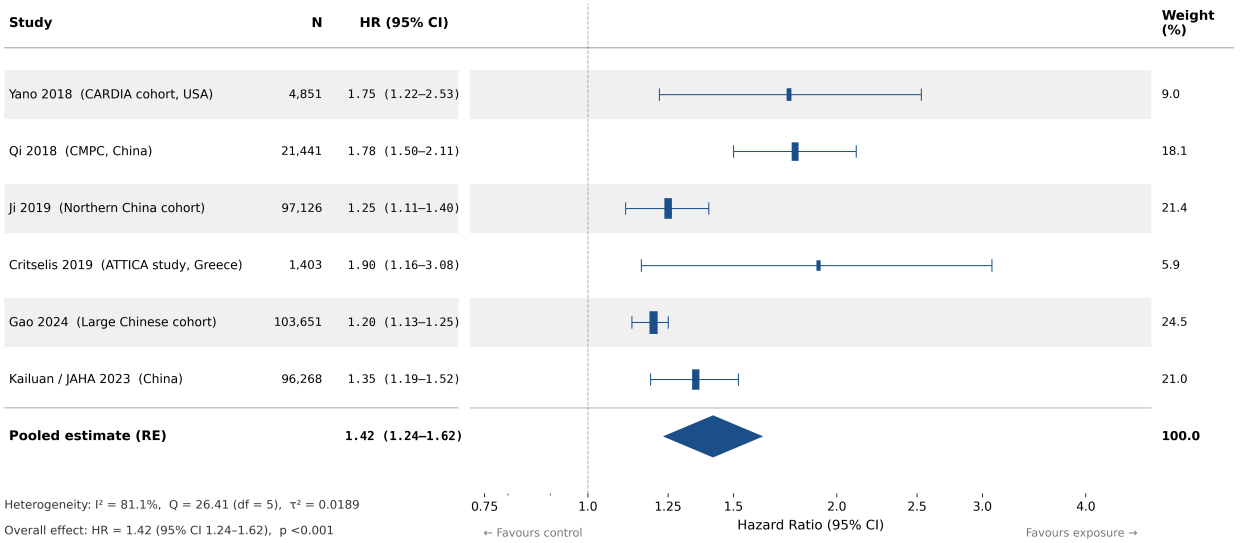

Figure 2. Forest plot: stage 1 hypertension and broad composite cardiovascular disease risk (HTN_BroadCVD subgroup, n = 6 studies). Squares represent individual study hazard ratio estimates, with area proportional to study weight. Diamond represents pooled hazard ratio. DerSimonian-Laird random-effects model. HR = hazard ratio; CI = confidence interval; RE = random effects.

HTN-Stroke and HTN-CVD Mortality (Narrative Subgroups)

For HTN-Stroke, Liu et al. (2020; N = 20,072) reported HR = 1.53 (95% CI: 1.20-1.95), directionally consistent with the primary pooled model. For cardiovascular mortality, Wu et al. (2021; HR = 1.69, 95% CI: 1.20-2.39) and Talaei et al. (2018; HR = 0.94, 95% CI: 0.81-1.11) yielded a pooled estimate of HR = 1.24 (95% CI: 0.70-2.20, p = 0.470); however, because only two studies contributed and heterogeneity was extreme (I^2 = 89.3%), this subgroup is more appropriately treated as exploratory narrative evidence than as a stable pooled estimate. The forest plot is presented in Figure 3.

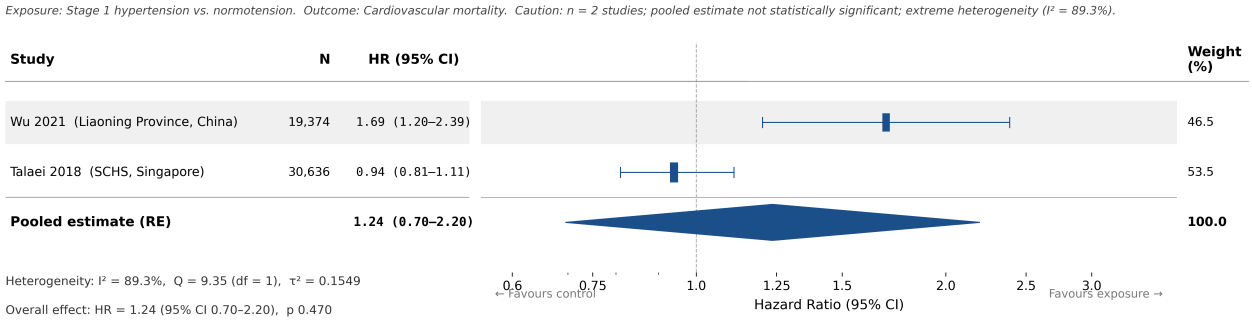

Figure 3. Forest plot: stage 1 hypertension and cardiovascular mortality (HTN_CVDMortality subgroup, n = 2 studies). Shown for transparency, but the subgroup should be interpreted cautiously because the pooled estimate is not statistically significant (p = 0.470), the study count is very small, and heterogeneity is extreme (I^2 = 89.3%). HR = hazard ratio; CI = confidence interval.

3.5 Meta-Analysis of Type 2 Diabetes and Cardiovascular Risk

T2D-Heart Failure Subgroup (Primary Pooled Model)

Four studies contributed: Shah et al. (2015), Rawshani et al. (2018), Rosengren et al. (2018), and Larsson et al. (2018). The pooled HR was **1.57 (95% CI: 1.38-1.78, p < 0.001; I^2 = 79.7%)**, representing a 57% increase in heart failure risk with T2DM. The highest estimate (Rosengren et al.,

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2018, HR = 2.07) reflected a younger male stratum; the two largest registry studies provided more conservative anchoring estimates. The forest plot is in Figure 4.

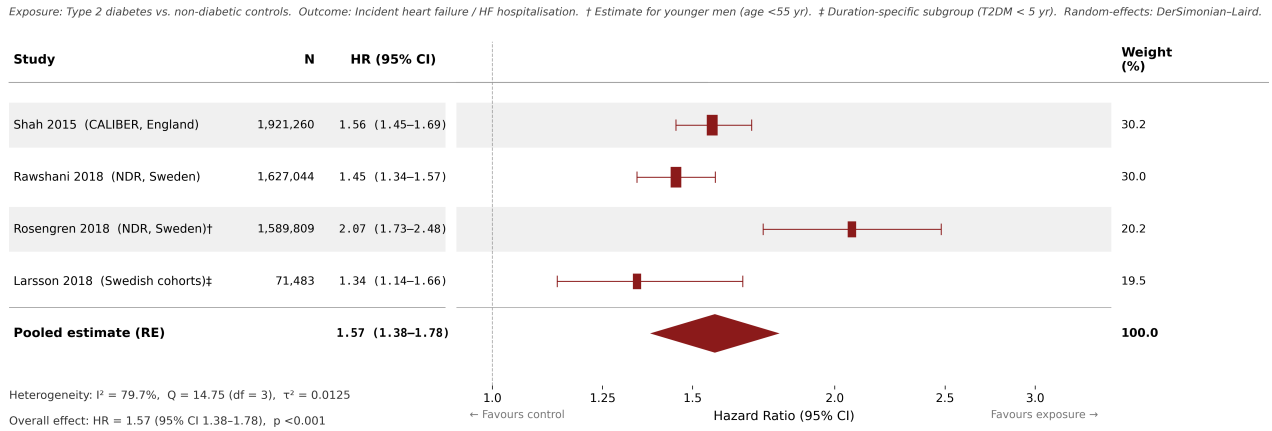
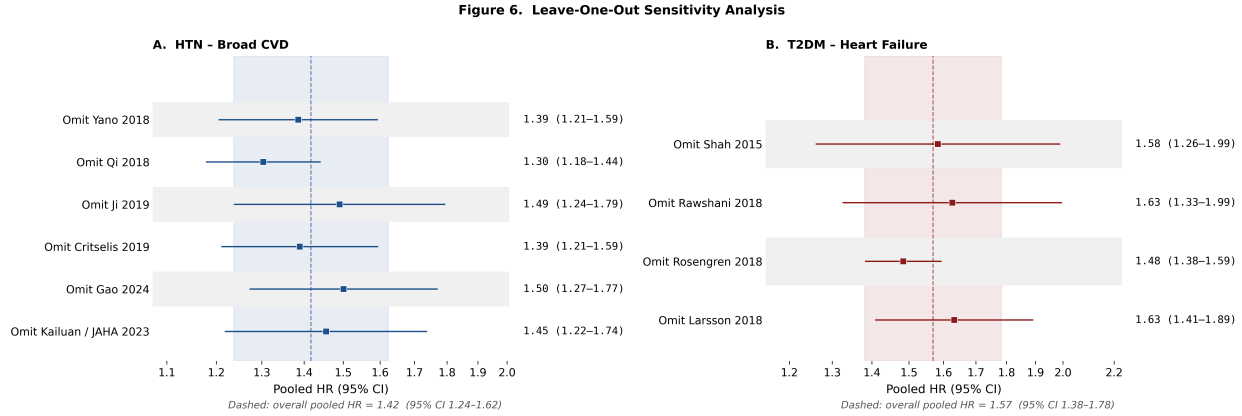


Figure 4. Forest plot: type 2 diabetes mellitus and incident heart failure risk (T2D_HF subgroup, n = 4 studies). Estimate specific to younger men (age <55 years). Duration-specific subgroup (T2DM duration <5 years). DerSimonian-Laird random-effects model. HR = hazard ratio; CI = confidence interval; NDR = National Diabetes Register.

Three T2DM subgroups were synthesized narratively. Gyldenkerne et al. (2023; N = 530,997) reported sub-HR = 1.91 (95% CI: 1.76-2.07) for composite CVD in an age 40-49 years stratum, representing the largest single estimate but not a domain-wide pooled effect. Tancredi et al. (2019; N = 2,605,199) reported HR = 1.42 (95% CI: 1.41-1.44) for major coronary events. Tancredi et al. (2015) reported HR = 1.14 (95% CI: 1.13-1.15) for cardiovascular cause-specific mortality. Across all three, the direction of association was positive, but inference is limited because each subgroup was represented by only one study.

3.6 Sensitivity, Influence, and Publication Bias Analyses

Leave-one-out analyses confirmed that the direction and statistical significance of both primary pooled models were robust to sequential study omission. For HTN-Broad CVD, sequential omission produced estimates of HR = 1.30 to 1.50 (Figure 5, Panel A). For T2D-HF, estimates ranged from HR = 1.48 to 1.63 (Figure 5, Panel B). Excluding Larsson et al. (2018) in sensitivity analysis yielded HR = 1.58 (95% CI: 1.37-1.83). Funnel plots for both pooled subgroups are presented in Figure 6 and should be interpreted cautiously because each subgroup contained fewer than 10 studies; formal Egger's regression was not applied (Page et al., 2021).



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Gland Surg
VOL-11 NO 1 (2026)
ISSN:2227-684X | E-ISSN:2227-8575

Figure 5. Leave-one-out sensitivity analysis for the HTN-Broad CVD primary subgroup (Panel A, n = 6 studies) and T2DM-Heart Failure primary subgroup (Panel B, n = 4 studies). Each row shows the pooled hazard ratio obtained when that study is sequentially excluded. Shaded band represents the 95% CI of the overall pooled estimate; dashed vertical line marks the pooled HR. All leave-one-out estimates retained statistical significance and directional consistency within the two primary pooled models.

Figure 7. Funnel Plots for Publication Bias Assessment

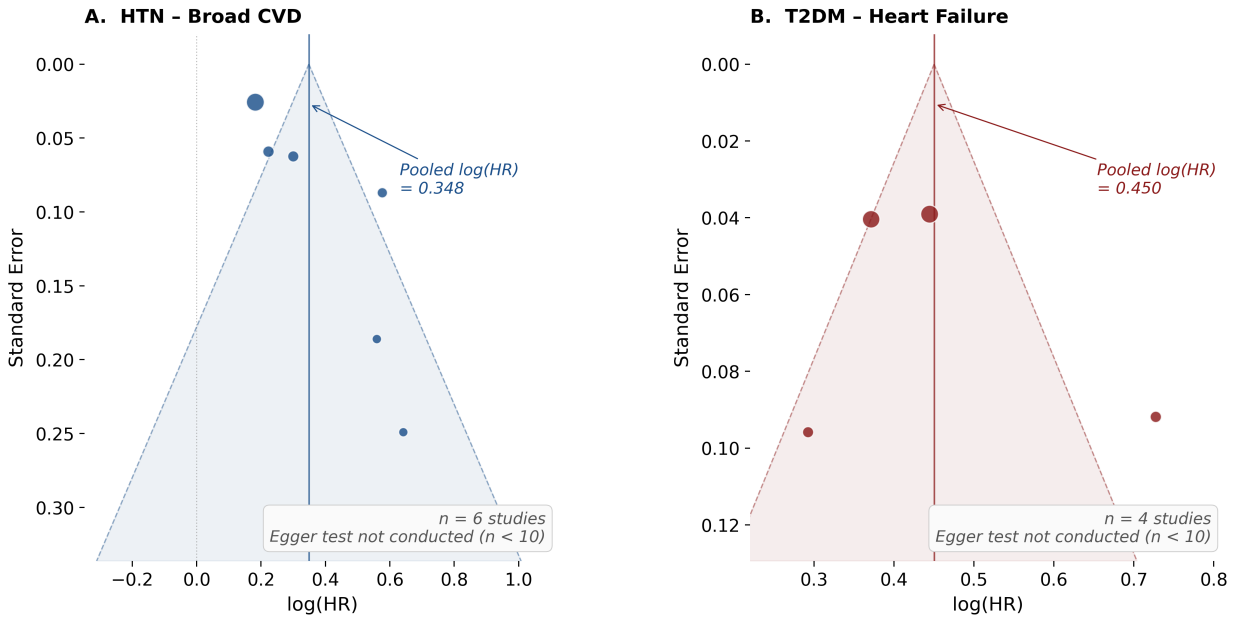

Figure 6. Contour-enhanced funnel plots for publication bias assessment: HTN-Broad CVD subgroup (Panel A, n = 6 studies) and T2DM-Heart Failure subgroup (Panel B, n = 4 studies). Point size is proportional to study precision (inverse-variance weight). Solid vertical line indicates the pooled log(HR); dashed lines indicate the 95% pseudo-confidence region. These plots are descriptive only because each subgroup contained fewer than 10 studies.

3.7 Summary of Results

Across all exposure domains and cardiovascular outcome families, the direction of association was generally positive; however, the strength of inference differed materially between pooled and narrative-only strata. The most robust quantitative findings were HR = 1.42 (95% CI: 1.24-1.62) for hypertension with broad CVD and HR = 1.57 (95% CI: 1.38-1.78) for T2DM with heart failure. The remaining subgroup estimates should be interpreted as supportive but less certain because they were based on one or two studies. Results are summarized in Table 5.

Table 5

Summary of Quantitative and Narrative Findings by Exposure Domain and Cardiovascular Outcome Family

Subgroup	Studies (n)	Effect estimate	95% CI	I2 (%)	p (overall)	Synthesis
HTN-Broad CVD	6	1.42	1.24-1.62	81.1	<0.001	Quantitative

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Gland Surg
VOL-11 NO 1 (2026)
ISSN:2227-684X | E-ISSN:2227-8575

HTN-Stroke	1	1.53	1.20-1.95	N/A	<0.001	Narrative only
HTN-CVD Mortality	2	1.24	0.70-2.20	89.3	0.470 (ns)	Exploratory narrative
T2D-Heart Failure	4	1.57	1.38-1.78	79.7	<0.001	Quantitative
T2D-Broad CVD	1	1.91*	1.76-2.07	N/A	<0.001	Narrative only
T2D-Coronary	1	1.42	1.41-1.44	N/A	<0.001	Narrative only
T2D-CVD Mortality	1	1.14	1.13-1.15	N/A	<0.001	Narrative only

Note. *sub-HR from competing-risk regression (Gyldenkerne et al., 2023; age 40-49 years stratum). HTN-CVD mortality is shown for completeness but should be interpreted as exploratory because only two studies contributed and heterogeneity was extreme. HTN = hypertension; T2DM = type 2 diabetes mellitus; CVD = cardiovascular disease; I^2 = heterogeneity statistic; N/A = not applicable (single study).

4. Discussion

4.1 Principal Findings

The review identified that the strongest quantitative evidence was on the finding that stage 1 hypertension was correlated with broad CVD and T2DM with heart failure. The exposure-specific outcome-stratified design was methodologically sound since only one global pooled estimate would have included clinically different exposures and endpoints. Simultaneously, the confidence of the inference was also not homogeneous throughout the review: two subgroups fulfilled the conditions of complete quantitative synthesis, and both of them demonstrated significant between-study heterogeneity ($I^2 > 79\%$).

4.2 Mechanistic Interpretation

The biological plausibility of the hypertension-CVD relationship is that slight increases in blood pressure can increase the speed of endothelial damage, arterial rigidity, maladaptive ventricular remodeling, and vulnerability of atherosclerotic plaque (Laurent et al., 2006). Nevertheless due to the high heterogeneity between cohorts, the magnitude of pooled effects sizes should be understood with caution and not believed to be an indicator of a single risk increment that can be transported across populations. The apparent differences between the largest Chinese cohort and smaller Western or Mediterranean cohort could be due to confounder adjustment, uptake of the treatment, the risk structure at the baseline or other unmeasured design variation, and not necessarily to the biological inconsistency. The T2DM-heart failure relationship (HR = 1.57) is also mechanistically reasonable, considering that there are other studies that demonstrate insulin resistance, lipotoxicity, mitochondrial dysfunction, and autonomic neuropathy to be linked with myocardial fibrosis and diastolic dysfunction (Sattar and Preiss, 2019). The younger men estimate of higher estimate by Rosengren et al. (2018, HR = 2.07) must be taken to be a subgroup-specific estimate and not the overall estimate of the entire T2DM population. Less dramatic modern estimates of coronary events and cardiovascular mortality in Scandinavian registries might be due to better multifactorial management risks, but these outcome

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Gland Surg
VOL-11 NO 1 (2026)
ISSN:2227-684X | E-ISSN:2227-8575

family members were not meta-analyzed in this study and should not be over-read.

4.3 Consistency with Prior Evidence and Guidelines

The overall HTN-wide CVD estimate (HR = 1.42) points in the right direction in accordance with the rationale that informed the 2017 ACC/AHA stage 1 hypertension classification (Carey et al., 2018). The T2DM-heart failure pooled estimate (HR = 1.57) also compares to the evidence presented in the past as summarized by MacDonald et al. (2008). The primary value of the current review is thus not to determine a single pooled cardiovascular effect, but to demonstrate that recent observational research still supports the selected exposures-outcomes relationships and indicates the disproportionality of the evidence base in different cardiovascular areas.

4.4 Clinical and Public-Health Implications

The results confirm attentive cardiometabolic risk evaluation in adults with stage 1 hypertension or T2DM, yet the data are not sufficient to make similar unequivocal conclusions regarding each cardiovascular endpoint family. In the case of hypertension, the most significant signal in this review is related to broad composite CVD; in relation to T2DM, this is heart failure. Wider practice guidelines (e.g. increased screening pathways, certain pharmacologic preferences) need to be based on focused guideline evidence and trial data rather than the direct inference of this review.

4.5 Strengths, Limitations, and Future Directions

The strengths are restriction to comparatively recent studies, predefined exposure-specific and outcome-family subgroups that did not result in indiscriminate over-pooling and strength of the two main pooled results of leave-one-out analyses. These are limitations such as observational designs that do not allow causal analysis, much residual heterogeneity in both pooled models, the absence of protocol registration, complete or incomplete reproducibility of the search strategy in the current manuscript text, and the fact that most of the analytical strata were only covered in one or two studies. The future studies ought to focus on harmonized joint-effect studies of comorbid hypertension and T2DM, improved standardization of endpoint definitions, and more standardized reporting formats that can allow quantitative synthesis of a wider spectrum of cardiovascular outcomes.

5. Conclusion

This selective subgroup meta-analysis systematic review reported the best quantitative evidence of an association of stage 1 hypertension with broad composite CVD risk (HR = 1.42, 95% CI: 1.24-1.62) and of T2DM with heart failure risk (HR = 1.57, 95% CI: 1.38-1.78). Directionally supportive but based mainly on narrative synthesis were evidence of stroke, cardiovascular mortality, coronary events, and general CVD in T2DM due to the small number of studies or non-comparability of the results. The manuscript, therefore, justifies the careful interpretation of exposure-specific cardiovascular risks as opposed to one ultimate integrated description of cardiometabolic risks in all outcome domains.

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ISSN:2227-684X | E-ISSN:2227-8575