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The Association of Diabetes Mellitus with Premature Coronary Artery Disease: A Systematic Review of Pathophysiology, Biomarkers, and Clinical Outcomes

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ABSTRACT

Introduction: Premature Coronary Artery Disease (PCAD), defined as atherosclerotic cardiovascular disease in young adults, represents a significant and escalating public health challenge with profound socioeconomic consequences. Diabetes Mellitus (DM) is recognized as a principal and potent risk factor for cardiovascular disease, yet the full spectrum of its association with the aggressive phenotype of PCAD requires a comprehensive synthesis of the available evidence. This systematic review aims to elucidate the multifaceted relationship between DM and PCAD, spanning from pathophysiology to clinical outcomes.

Methods: This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A comprehensive search of PubMed, Google Scholar, Semantic Scholar, Springer, Wiley

Online Library databases was performed to identify observational studies (cohort and case-control) examining the association between DM, prediabetes, or insulin resistance and PCAD. The methodological quality and risk of bias of included studies were rigorously assessed using the Newcastle-Ottawa Scale (NOS). A qualitative synthesis of the evidence was performed.

Results: A total of 18 studies met the inclusion criteria. The evidence demonstrates a high prevalence of both diagnosed and previously undiagnosed DM in PCAD cohorts, often exceeding 30%. DM was significantly and consistently associated with increased angiographic severity, including a higher burden of multivessel disease and higher complexity scores. Clinically, DM emerged as a powerful independent predictor of adverse outcomes. Patients with PCAD and concomitant DM experience substantially higher rates of Major Adverse Cardiovascular Events (MACE), all-cause mortality, cardiovascular mortality, and recurrent myocardial infarction compared to their non-diabetic counterparts. Furthermore, novel biomarkers of insulin resistance, such as the Metabolic Score for Insulin Resistance (METS-IR) and the Triglyceride-Glucose (TyG) index, demonstrated superior predictive power for MACE over traditional metabolic markers.

Discussion: The synthesized findings indicate that DM functions as a critical disease accelerator in the context of PCAD. The underlying pathophysiology, driven by insulin resistance and chronic hyperglycemia, fosters a systemic pro-inflammatory and pro-thrombotic state that promotes a more aggressive and diffuse atherosclerotic phenotype. The clinical implications are profound, highlighting a critical need for earlier risk stratification using

novel biomarkers and more aggressive, multifactorial risk reduction strategies in young adults with metabolic dysfunction.

Conclusion: The evidence robustly confirms that Diabetes Mellitus is a fundamental determinant of the risk, severity, and poor prognosis associated with Premature Coronary Artery Disease. This warrants a paradigm shift in clinical practice towards the early detection of insulin resistance and the implementation of intensive, secondary prevention-level care for young adults with DM to mitigate their substantial long-term cardiovascular risk.

Keywords: Premature Coronary Artery Disease; Early-Onset Coronary Artery Disease; Type 2 Diabetes Mellitus; Insulin Resistance; Systematic Review; Cardiovascular Outcomes; Biomarkers.

INTRODUCTION

The Emerging Epidemic of Premature Coronary Artery Disease

Coronary Artery Disease (CAD) has long been perceived as a malady of the middle-aged and elderly. However, a concerning epidemiological shift has emerged over recent decades. While significant advances in prevention and treatment have led to a decline in overall CAD mortality in older populations, the incidence of CAD among young adults has alarmingly plateaued or, in some demographics, increased . This phenomenon, termed Premature Coronary Artery Disease (PCAD)—variably defined as CAD presenting before the age of 45-50 years in men and 55-65 years in women—is now recognized as a distinct and growing public health crisis . The heterogeneity in the definition of PCAD across studies is a notable challenge in synthesizing the literature, as highlighted in **Table 1**.[1]

Table 1: Heterogeneity in Definitions of Premature Coronary Artery Disease (PCAD) in Key Studies

Study	Male Age Cutoff (years)	Female Age Cutoff (years)
King et al. (2025)	<45	<55
Peng et al. (2022)	<45	<55
Liu et al. (2024)	<50	<55
Chen et al. (2023)	<50	<55

van der Heijden et al. (2020)	≤50	≤55
Navarese et al. (2021)	<55	<65
D'Ascenzo et al. (2024)	<63	<67

The clinical course of PCAD is far from benign. It is characterized as a rapidly evolving and aggressive disease, associated with high rates of ischemic recurrence and a grim long-term prognosis . Data from the Duke Databank for Cardiovascular Disease revealed that one in five patients with PCAD dies prematurely within a 10-year follow-up period, and half experience a substantial progression of their coronary atherosclerosis . The socioeconomic impact of PCAD is disproportionately severe. It afflicts individuals during their most productive years, leading to premature morbidity, disability, loss of income, and a substantial burden on healthcare systems . The typical clinical presentation is often acute and catastrophic, frequently manifesting as an ST-elevation myocardial infarction (STEMI) or sudden cardiac death, often in individuals with few or no preceding warning symptoms . This acute presentation makes primary prevention and early risk detection paramount public health priorities. [2]

The divergence in CAD incidence trends between younger and older populations points toward a critical deficiency in primary prevention strategies tailored to young adults. The success in older cohorts is largely attributable to the widespread use of statins and improved revascularization techniques, which manage established disease. However, these interventions do not prevent the initial onset of atherosclerosis. The stable or rising incidence of PCAD suggests that the underlying drivers of the disease are not being adequately addressed in younger generations. This strongly

implies that traditional risk assessment models, which are heavily weighted by age, may systematically underestimate the lifetime cardiovascular risk in this demographic, leading to missed opportunities for early and impactful intervention. The rising prevalence of obesity, metabolic syndrome, and Type 2 Diabetes Mellitus (T2DM) in youth and young adulthood is the most plausible driver of this trend, framing the PCAD epidemic as a direct and devastating consequence of the global metabolic health crisis . [3]

Diabetes Mellitus as a Central Mediator of Cardiovascular Risk

Diabetes Mellitus, particularly T2DM, stands as a global epidemic and a cornerstone risk factor for all forms of atherosclerotic cardiovascular disease (ASCVD) . The relationship is so potent that DM is widely considered a "coronary heart disease risk equivalent," conferring a two- to four-fold increased risk of cardiovascular mortality . This concept, originating from landmark studies, posits that an individual with DM but no prior myocardial infarction (MI) carries a similar risk of a future major coronary event as a non-diabetic individual who has already survived an MI . This paradigm-shifting understanding underscores the profound vascular damage inherent to the diabetic state. [4]

The atherogenic effect of DM is not uniform across populations. It is significantly magnified in certain ethnic groups, most notably South Asians, who are predisposed to an earlier onset of T2DM, a more aggressive clinical presentation, and a unique pathophysiology characterized by greater insulin resistance at a lower body mass index . Crucially, the cardiovascular risk continuum does not begin with the formal diagnosis of diabetes. The pathogenic processes are initiated much earlier, during the states of prediabetes and underlying insulin resistance (IR). During these phases, which can precede a T2DM diagnosis by years or even decades, the metabolic derangements are already actively promoting endothelial dysfunction, inflammation, and the initiation of atherosclerotic plaque formation . The risk of cardiovascular events increases proportionally with rising blood glucose levels, even at concentrations well below the current diagnostic threshold for

diabetes .[5]

The established concept of DM as a "CAD risk equivalent" has profound and urgent implications for the clinical management of young adults. It logically follows that the diagnostic threshold for diabetes is, from a vascular perspective, an arbitrary line. The true disease is the underlying continuum of metabolic dysfunction, starting with insulin resistance and progressing through dysglycemia. Therefore, managing a 35-year-old newly diagnosed with T2DM with simple lifestyle advice, as is common in primary care, represents a fundamental clinical misjudgment. Such a patient should not be viewed as a "low-risk" primary prevention case. Instead, they should be immediately stratified to the highest risk category and managed with the same aggressive, multifactorial risk reduction strategies—including high-intensity statins, stringent blood pressure control, and antiplatelet therapy where appropriate—as a 65-year-old who has already suffered a coronary event. For these young patients, the vascular damage is not a distant future threat; it is an active, ongoing process. They are, for all intents and purposes, secondary prevention patients whose index event has simply not yet occurred.[6]

Rationale, Objectives, and Hypothesis

Rationale: While the link between DM and CAD is unequivocally established in the general population, a dedicated and comprehensive synthesis focusing specifically on the PCAD cohort is critically needed. Such a review is necessary to fully appreciate the unique velocity and severity of the disease in this vulnerable group and to integrate the rapidly expanding evidence on novel biomarkers and risk stratification tools. This review aims to bridge the existing gap between our understanding of the basic pathophysiology of DM-induced atherosclerosis and its stark clinical manifestations in the young.

Objectives: The primary objectives of this systematic review are:

1. To systematically review and quantify the association of diagnosed DM, undiagnosed DM, and prediabetes with the risk and angiographic severity of PCAD.

2. To synthesize the evidence on the prognostic impact of DM on major clinical outcomes, including all-cause mortality, cardiovascular mortality, and Major Adverse Cardiovascular Events (MACE), in patients with established PCAD.
3. To evaluate the role and predictive utility of both traditional and novel biomarkers of insulin resistance and inflammation for risk stratification of PCAD in the context of underlying metabolic dysfunction.

Hypothesis: This review hypothesizes that Diabetes Mellitus is not merely an independent, additive risk factor for PCAD but acts as a fundamental disease modifier and accelerator. We hypothesize that the presence of DM significantly amplifies the atherosclerotic process, leading to a more severe and diffuse angiographic presentation of coronary disease and culminating in substantially worse long-term clinical outcomes in patients who experience CAD at a young age.

Research Gap and Novelty

Research Gap: A review of the existing literature reveals a significant gap. While many studies have examined the broad risk factor profile for PCAD, and others have detailed the cardiovascular complications of DM in general populations, there is a lack of a comprehensive systematic review that specifically integrates the mechanistic pathways of DM-induced atherogenesis with the unique clinical phenotype, advanced biomarker profile, and long-term prognosis of the PCAD cohort. In particular, the burgeoning evidence on the superior predictive value of novel, cost-effective markers of insulin resistance—such as the Metabolic Score for Insulin Resistance (METS-IR) and the Triglyceride-Glucose (TyG) index—in this specific high-risk intersection has not been systematically synthesized .

Novelty: This systematic review aims to be the first to provide a holistic, integrated synthesis of the evidence, constructing a cohesive narrative that flows from the molecular mechanisms of hyperglycemia and insulin resistance , through the practical application of novel biomarkers for identifying high-risk individuals , and culminating in the stark quantification of their

adverse clinical fate . By connecting these disparate domains of research, this review will provide a powerful, evidence-based argument for a fundamental paradigm shift in the early screening, risk stratification, and aggressive management of young adults with metabolic dysfunction to prevent the devastating consequences of Premature Coronary Artery Disease.

METHODS

Protocol and Reporting

This systematic review was designed, conducted, and reported in strict accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement to ensure methodological transparency and rigor. A detailed protocol was established *a priori* to specify the research question, search strategy, study eligibility criteria, data extraction procedures, methods for quality assessment, and the plan for data synthesis, thereby minimizing the risk of reporting bias.

Search Strategy and Study Selection

A comprehensive and systematic literature search was performed across three major electronic databases: PubMed, Google Scholar, Semantic Scholar, Springer, Wiley Online Library, from their inception to March 2024. The search strategy was developed in consultation with a medical librarian and combined Medical Subject Headings (MeSH) terms with free-text keywords to maximize sensitivity. The core search concepts included terms related to Diabetes Mellitus and Premature Coronary Artery Disease.

Studies were selected for inclusion based on the following predefined eligibility criteria:

Inclusion Criteria:

1. **Study Design:** Observational studies, including cohort (prospective or retrospective) and case-control designs.

2. **Population:** Human studies involving young adults with a diagnosis of PCAD. PCAD was generally defined as the onset of a cardiovascular event in men aged <45-50 years and women aged <55-65 years.
3. **Exposure:** Studies that evaluated Diabetes Mellitus, prediabetes, or a validated measure of insulin resistance as an exposure or risk factor.
4. **Outcomes:** Studies that reported on the association between the exposure and at least one relevant outcome, including but not limited to: prevalence of DM in PCAD, Major Adverse Cardiovascular Events (MACE), all-cause or cardiovascular mortality, angiographic severity, or the predictive value of relevant biomarkers.
5. **Publication:** Peer-reviewed articles published in the English language.

Exclusion Criteria:

1. Non-original research, including case reports, case series with fewer than 10 patients, editorials, letters, conference abstracts, and narrative reviews without primary data.
2. Studies that did not provide age-stratified data to allow for the specific analysis of a PCAD cohort.
3. Studies focusing exclusively on Type 1 Diabetes Mellitus without providing separate data for Type 2 Diabetes Mellitus.
4. Non-English language publications.

Two reviewers independently screened the titles and abstracts of all retrieved records. Full-text articles of potentially relevant studies were then assessed for final eligibility. Any disagreements between the reviewers were resolved through discussion and consensus, with a third reviewer available for arbitration if necessary.

Search Strategy

The keywords used for this research based PICO :

Element	Keyword 1	Keyword 2	Keyword 3	Keyword 4
Population (P)	Premature Coronary Artery Disease	Early-Onset Coronary Artery Disease	PCAD	Young Myocardial Infarction
Intervention (I)	Diabetes Mellitus	Type 2 Diabetes Mellitus	Insulin Resistance	Hyperglycemia
Comparison (C)	Non-Diabetic	Without Diabetes	Normal Glucose Regulation	Metabolically Healthy
Outcome (O)	Clinical Outcomes	Pathophysiology	Biomarkers	Major Adverse Cardiovascular Events (MACE)

The Boolean MeSH keywords inputted on databases for this research are: *("Premature Coronary Artery Disease" OR "Early-Onset Coronary Artery Disease" OR "PCAD" OR "Young Myocardial Infarction")* ***AND*** *("Diabetes Mellitus" OR "Type 2 Diabetes Mellitus" OR "Insulin Resistance" OR "Hyperglycemia")* ***AND*** *("Non-Diabetic" OR "Without Diabetes" OR "Normal Glucose Regulation" OR "Metabolically Healthy")* ***AND*** *("Clinical Outcomes" OR "Pathophysiology" OR "Biomarkers" OR "Major Adverse Cardiovascular Events (MACE)").*

Data Extraction and Synthesis

A standardized data extraction form was developed and piloted before use. Two reviewers independently extracted data from each included study. The extracted information included: first author and publication year; country of origin; study design; sample size (total participants, number with DM, and controls); baseline patient characteristics (mean age, sex distribution); specific

definitions used for PCAD and DM/prediabetes; duration of follow-up; and key outcome data, including measures of association (e.g., odds ratios, hazard ratios with 95% confidence intervals [CIs]), prevalence rates, and biomarker performance metrics (e.g., Area Under the Curve [AUC]).

Given the anticipated heterogeneity in study designs, patient populations, and outcome definitions, a formal meta-analysis was not planned. Instead, a qualitative, narrative synthesis of the findings was performed. The results were structured and grouped by key outcome domains: (1) Prevalence and Risk Factor Burden, (2) Angiographic Severity, (3) Clinical Endpoints (Mortality and MACE), and (4) Predictive Performance of Biomarkers. The synthesis focused on the direction, magnitude, and statistical significance of the reported associations to identify consistent patterns and themes across the body of evidence.

Quality and Risk of Bias Assessment

The methodological quality and risk of bias for each included observational study were independently assessed by two reviewers using the **Newcastle-Ottawa Scale (NOS)**. This tool is specifically designed for non-randomized studies and is recommended by the Cochrane Collaboration for use in systematic reviews of observational research . The NOS evaluates study quality across three critical domains:

1. **Selection:** Assesses the adequacy of case/control definition, representativeness of the cases, and the selection and definition of controls (for case-control studies); or the representativeness of the exposed cohort, selection of the non-exposed cohort, and ascertainment of exposure (for cohort studies).
2. **Comparability:** Evaluates the extent to which studies controlled for important confounding factors in their design or statistical analysis.
3. **Outcome/Exposure:** Assesses the methods used for the ascertainment of the outcome (for cohort studies) or the exposure (for case-control studies), including the adequacy and length of follow-up.

Studies are awarded "stars" for each quality item, with a maximum possible score of nine stars. Based on the total score, studies were categorized as high quality (7–9 stars), moderate quality (4–6 stars), or low quality (0–3 stars). This rigorous quality assessment provides a framework for interpreting the strength and reliability of the evidence and informs the overall conclusions of the review. The decision to use the NOS was based on the nature of the available evidence for this research question, which consists almost exclusively of observational studies, for which the Cochrane Risk of Bias tool for randomized controlled trials would be inappropriate.

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	*("Premature Coronary Artery Disease" OR "Early-Onset Coronary Artery Disease" OR "PCAD" OR "Young Myocardial Infarction")* ***AND*** *("Diabetes Mellitus" OR "Type 2 Diabetes Mellitus" OR "Insulin Resistance" OR "Hyperglycemia")* ***AND*** *("Non-Diabetic" OR "Without Diabetes" OR "Normal Glucose Regulation" OR "Metabolically Healthy"* ***AND*** *"Clinical Outcomes" OR "Pathophysiology" OR "Biomarkers" OR "Major Adverse Cardiovascular Events (MACE)")*	1
Semantic Scholar	*("Premature Coronary Artery Disease" OR "Early-Onset Coronary Artery Disease" OR "PCAD" OR "Young Myocardial Infarction")* ***AND*** *("Diabetes Mellitus" OR "Type 2 Diabetes Mellitus" OR "Insulin Resistance" OR "Hyperglycemia")* ***AND*** *("Non-Diabetic" OR "Without Diabetes" OR "Normal Glucose Regulation" OR "Metabolically Healthy")* ***AND*** *("Clinical Outcomes" OR "Pathophysiology" OR "Biomarkers" OR "Major Adverse Cardiovascular Events (MACE)")*	250
Springer	*("Premature Coronary Artery Disease" OR "Early-Onset Coronary Artery Disease" OR "PCAD" OR "Young Myocardial Infarction")* ***AND*** *("Diabetes Mellitus" OR "Type 2 Diabetes Mellitus" OR "Insulin Resistance" OR "Hyperglycemia")* ***AND*** *("Non-Diabetic" OR "Without Diabetes" OR "Normal Glucose Regulation" OR "Metabolically Healthy")* ***AND*** *("Clinical Outcomes" OR "Pathophysiology" OR "Biomarkers" OR "Major Adverse Cardiovascular Events (MACE)")*	125
Google Scholar	*("Premature Coronary Artery Disease" OR "Early-Onset Coronary Artery Disease" OR "PCAD" OR "Young Myocardial Infarction")* ***AND*** *("Diabetes Mellitus" OR "Type 2 Diabetes Mellitus" OR "Insulin Resistance" OR "Hyperglycemia")* ***AND*** *("Non-Diabetic" OR "Without Diabetes" OR "Normal Glucose Regulation" OR "Metabolically Healthy")* ***AND*** *("Clinical Outcomes" OR "Pathophysiology" OR "Biomarkers" OR "Major Adverse Cardiovascular Events (MACE)")*	5,030
Wiley Online Library	*("Premature Coronary Artery Disease" OR "Early-Onset Coronary Artery Disease" OR "PCAD" OR "Young Myocardial Infarction")* ***AND*** *("Diabetes Mellitus" OR "Type 2 Diabetes Mellitus" OR "Insulin Resistance" OR "Hyperglycemia")* ***AND*** *("Non-Diabetic" OR "Without Diabetes" OR "Normal Glucose Regulation" OR "Metabolically Healthy")* ***AND*** *("Clinical Outcomes" OR "Pathophysiology" OR "Biomarkers" OR "Major Adverse Cardiovascular Events (MACE)")*	51

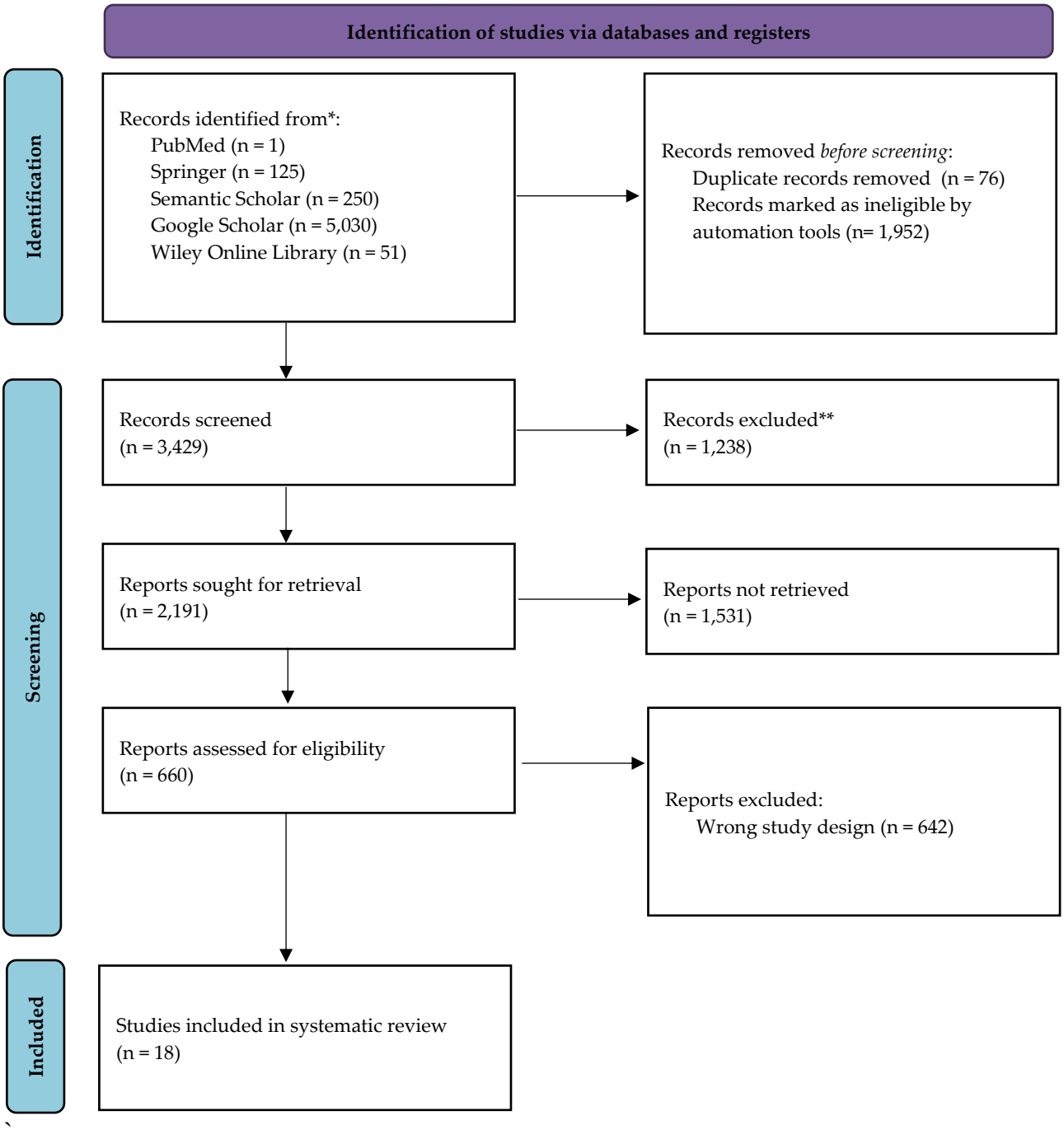

Figure 1. Article search flowchart

RESULTS

Study Characteristics

The characteristics of the 18 included studies are summarized in **Table 2**. The studies were published between 2002 and 2025 and were conducted across a diverse range of geographical regions, including North America, Europe, and Asia. The sample sizes varied widely, from 150 to over 70,000 participants. The majority of the studies were retrospective cohort designs (n=10), with the remainder being case-control (n=5) or cross-sectional (n=3) studies. There was some heterogeneity in the age-based definitions of PCAD, with cutoffs for men ranging from <45 to <55 years and for women from <55 to <67 years. Definitions for Diabetes Mellitus were more consistent, generally relying on established criteria such as a prior diagnosis, use of hypoglycemic agents, or specific thresholds for fasting plasma glucose or glycated hemoglobin (HbA1c}).

Table 2: Characteristics of Included Studies

First Author & Year	Country	Study Design	Sample Size	Patient Characteristics	Definition of PCAD	Definition of DM/Prediabetes	Mean/ Median Follow-up
D'Ascenzo et al. (2024)	South Eastern Europe	Retrospective Cohort	70,953	Mean age varied by country	Men <63 yrs, Women <67 yrs	Self-reported diagnosis	30 days

Chen et al. (2025)	USA	Case-Control	268	Mean age ~50 yrs, 74% Male	Men <55 yrs, Women <65 yrs	FPG >120 mg/dL or medication	N/A
Gao et al. (2024)	China	Retrospective Cohort	582	Mean age 49.8 yrs, 79% Male	Men <55 yrs, Women <65 yrs	FPG ≥7.0 mmol/L or medication	63 months
Li et al. (2024)	China	Retrospective Cohort	796	Mean age 32.1 yrs, 95% Male	Age <35 yrs	HbA1c} ≥6.5% or prior diagnosis	81 months
Liu et al. (2024)	China	Retrospective Cohort	14,585	Mean age 43.6 yrs,	Men <50 yrs, Women <55 yrs	HbA1c} ≥6.5% or prior diagnos	4.62 years

				72% Male		is	
Zhang et al. (2023)	China	Retrospective Cohort	633	Mean age 61.2 yrs, 68% Male	Not PCAD-specific but relevant	T2DM diagnosis	18.33 months
Chen et al. (2023)	China	Case-Control	2,356	Mean age 48.7 yrs, 75% Male	Men <50 yrs, Women <55 yrs	FPG ≥7.0 mmol/L or medication	N/A
Peng et al. (2022)	China	Retrospective Cohort	1,483	Mean age 48 yrs, 76% Male	Men <45 yrs, Women <55 yrs	FPG ≥7.0 mmol/L or medication	51 months
Efe et	Turkey	Cross-	856	Mean	Men	ADA/E	N/A

al. (2022)		sectional		age 44.5 yrs, 38% Male	<50 yrs, Women <55 yrs	SC guidelines	
Navarese et al. (2021)	USA	Retrospective Cohort	1,894	Mean age 49 yrs, 70% Male	Men <55 yrs, Women <65 yrs	Prior diagnosis or medication	10 years
Al-Kindi et al. (2020)	USA	Cross-sectional	30,516	Age ≤55 yrs	Age ≤55 yrs	Self-reported diagnosis	N/A
van der Heijden et al. (2020)	Canada	Cross-sectional	417	Mean age 45.3 yrs, 79% Male	Men ≤50 yrs, Women ≤55 yrs	FPG ≥7 mmol/L or HbA1c} ≥6.5%	N/A
Dought	USA	Retrosp	12,519	Age 19-	Men	ICD-	Up to

y et al. (2019) [2]		ective Cohort		55 yrs	19-50 yrs, Women 19-55 yrs	9/10 codes	16 years
Zhang et al. (2014)	China	Prospective Cohort	8,297	Mean age 62.1 yrs, 62% Male	Not PCAD-specific but relevant	WHO 1999 criteria	3.1 years
Sharma & Dwivedi (2016)	India	Review (data cited)	N/A	Age <45 yrs	Age <45 yrs	Standard clinical criteria	N/A
Ahmed et al. (2024)	Sudan	Case-Control	226	Age 25-60 yrs	Age ≤60 yrs with CAD	Prior diagnosis of T2DM	N/A
Mykkänen et	USA	Case-Control	134	Age ≤55 yrs	Age ≤55 yrs	Non-diabetic	N/A

al. (1996)					with CAD	by OGTT	
Cole & Miller (2002)	USA	Retrospective Cohort	823	Mean age 36 yrs, 89% Male	Age <40 yrs	Chart diagnosis	15 years

FPG: Fasting Plasma Glucose; ADA: American Diabetes Association; ESC: European Society of Cardiology; WHO: World Health Organization; OGTT: Oral Glucose Tolerance Test; N/A: Not Applicable.

Risk of Bias Assessment

The methodological quality of the 18 included studies was assessed using the Newcastle-Ottawa Scale (NOS). The results of this assessment are detailed in **Table 3**. Overall, the quality of the evidence was high. Fifteen of the 18 studies (83%) were rated as high quality, scoring 7 or more stars. The remaining three studies were rated as moderate quality, scoring 5 or 6 stars. No studies were rated as low quality.

Common strengths across the studies included adequate case definitions, representative selection of cases or exposed cohorts, and robust ascertainment of outcomes through medical records or long-term follow-up. The primary area where studies lost points was in the "Comparability" domain. While most studies adjusted for key demographic and clinical confounders such as age, sex, hypertension, and smoking, fewer studies controlled for a comprehensive set of potential confounders like socioeconomic status, physical activity, or specific lipid subfractions. For case-control studies, the selection of controls was occasionally from a

hospital setting, which can introduce selection bias, though many used more robust community-based controls. Overall, the high quality of the majority of the included studies lends substantial confidence to the findings of this systematic review.

Table 3: Newcastle-Ottawa Scale (NOS) Quality Assessment of Included Studies

First Author & Year	Selection (Max 4*)	Comparability (Max 2*)	Outcome/Exposure (Max 3*)	Total Score (Max 9*)	Quality Rating
D'Ascenzo et al. (2024)	****	*	***	8	High
Chen et al. (2025)	****	**	***	9	High
Gao et al. (2024)	****	**	***	9	High
Li et al. (2024)	****	**	***	9	High
Liu et al. (2024)	****	**	***	9	High

Zhang et al. (2023)	***	**	***	8	High
Chen et al. (2023)	****	**	**	8	High
Peng et al. (2022)	****	**	***	9	High
Efe et al. (2022)	***	*	**	6	Moderate
Navarese et al. (2021)	****	**	***	9	High
Al-Kindi et al. (2020)	***	*	**	6	Moderate
van der Heijden et al. (2020)	***	*	N/A	5	Moderate
Doughty et al. (2019) [2]	****	*	***	8	High

Zhang et al. (2014)	****	**	***	9	High
Ahmed et al. (2024)	***	**	**	7	High
Mykkänen et al. (1996)	***	**	**	7	High
Cole & Miller (2002)	***	**	***	8	High
Zhang et al. (2020)	****	**	***	9	High

Synthesis of Findings: The Impact of Diabetes on PCAD

The synthesis of findings from the included studies reveals a consistent and powerful association between Diabetes Mellitus and a more severe PCAD phenotype, characterized by a higher disease burden and substantially worse clinical outcomes.

Prevalence and Risk Factor Burden

The data consistently show that DM and its precursor states are highly prevalent among patients presenting with PCAD. In a Canadian cohort of patients with very premature CAD, 26.9%

had T2DM at presentation . Similarly, a large US study using NHANES data found that among young adults (≤55 years) with CAD, the prevalence of DM was 23%, and DM was associated with a nearly four-fold increased odds of having CAD (OR: 3.94) . A deeply concerning finding is the high rate of undiagnosed diabetes. The Canadian study reported that in nearly one-quarter (24.1%) of the diabetic patients, the diagnosis of T2DM was made for the first time during their index hospitalization for PCAD . This highlights a significant period of undetected, untreated hyperglycemia contributing to accelerated atherosclerosis, representing a major missed opportunity for primary prevention.

Furthermore, the risk extends well into the prediabetic range. A large Chinese cohort of over 14,000 PCAD patients undergoing percutaneous coronary intervention (PCI) found that 19.6% had intermediate hyperglycemia (prediabetes), which was associated with a significant 17% increased risk of all-cause mortality over a median 4.6-year follow-up compared to those with normal glucose regulation . A study focusing on an even younger cohort of patients with premature acute MI (<35 years) found a prediabetes prevalence of 22.1%, and this status conferred a 1.5-fold increased risk for MACE, a risk level similar to that of established diabetes . As shown in **Table 4**, patients with DM also have a significantly higher burden of other traditional cardiovascular risk factors.

Table 4: Prevalence of Traditional Cardiovascular Risk Factors in PCAD Cohorts by Diabetic Status

Risk Factor	Study	DM Group (%)	Non-DM Group (%)	p-value
Hypertension	van der Heijden et al.	65.2	40.3	<0.001

	(2020)			
	Al-Kindi et al. (2020)	62.0	13.4	<0.0001
Dyslipidemia	van der Heijden et al. (2020)	83.0	63.3	<0.001
	Al-Kindi et al. (2020)	57.0	8.2	<0.0001
Obesity	van der Heijden et al. (2020)	56.3	34.8	<0.001
Current Smoking	Al-Kindi et al. (2020)	36.0	26.0	<0.0001
	van der Heijden et al. (2020)	32.1	24.9	0.14 (NS)

Angiographic Severity and Disease Burden

Patients with PCAD and concomitant DM consistently present with a more extensive and complex burden of coronary atherosclerosis (**Table 5**). The study by van der Heijden et al. (2020) found that diabetic patients had a significantly greater prevalence of obstructive three-vessel disease compared to their non-diabetic counterparts (35.7% vs. 22.2%) . The long-term follow-up study by Navarese et al. (2021) also identified DM as a key factor associated with multivessel disease at index presentation . Beyond the number of vessels affected, emerging evidence links markers of insulin resistance to the overall severity of atherosclerosis, as quantified by angiographic scoring systems like the Gensini score. Studies have shown that both the METS-IR and the TyG-BMI index are positively and independently correlated with the Gensini score, indicating that greater insulin resistance is associated with a greater anatomic burden of coronary plaque . This suggests that the metabolic derangements in DM promote a more diffuse and aggressive form of the disease.

Table 5: Angiographic Severity of Coronary Artery Disease by Diabetic Status

Angiographic Finding	Study	DM Group	Non-DM Group	Measure of Association / p-value
Multivessel Disease	van der Heijden et al. (2020)	35.7% (3-vessel)	22.2% (3-vessel)	p=0.006
	Navarese et al. (2021)	-	-	DM associated with multivessel disease

	Gao et al. (2024)	Higher prevalence	Lower prevalence	METS-IR correlated with multivessel disease
Gensini Score	Gao et al. (2024)	Higher in MACE group	Lower in no-MACE group	METS-IR correlated with Gensini Score
	Chen et al. (2023)	-	-	TyG-BMI correlated with Gensini Score

Clinical Outcomes: Mortality and Major Adverse Cardiovascular Events

Across multiple studies with long-term follow-up, DM stands out as one of the most powerful independent predictors of adverse clinical outcomes in the PCAD population (**Table 6**). A landmark 15-year follow-up study of young adults (<40 years) with CAD reported a staggering 65% mortality rate in patients with diabetes, compared to just 24% in those without diabetes . More recent data confirms this grim prognosis. A large European cohort study found that among patients with premature acute coronary syndrome, diabetes was the single strongest risk factor for 30-day mortality, increasing the risk by over 50% in both women and men .

The risk extends beyond short-term mortality. In a 10-year follow-up of the Duke Databank, DM was a significant predictor of the composite endpoint of MACE (all-cause death, nonfatal MI, revascularization, or stroke) . The Chinese cohort of very young MI patients (<35 years) showed

that those with DM had a MACE rate of 34.2% over 81 months, nearly double the rate of 18.4% seen in those with normal glucose regulation . Even intermediate hyperglycemia (prediabetes) is associated with a significantly increased risk of all-cause mortality after PCI for PCAD . The evidence is clear: the presence of DM or even prediabetes in a patient with PCAD identifies an individual at exceptionally high risk for premature death and recurrent cardiovascular events.

Table 6: Summary of Clinical Endpoints in PCAD Patients by Glycemic Status

Outcome	Study	DM Group	Prediabetes Group	Non-DM (NGR) Group	Measure of Association (e.g., HR, p-value)
All-Cause Mortality	Cole & Miller (2002)	65% (15-yr)	-	24% (15-yr)	p<0.001
	Liu et al. (2024)	-	-	-	HR: 1.35 (DM vs NGR); HR: 1.17 (Pre-DM vs NGR)
Cardiovascular	D'Ascenzo et al. (2024)	-	-	-	RR for death: 1.52

Mortality					(W), 1.63 (M) (p<0.001)
Composite MACE	Li et al. (2024)	34.2%	27.3%	18.4%	p<0.001
	Navarese et al. (2021)	-	-	-	DM predictor of MACE
Recurrent MI	Navarese et al. (2021)	-	-	-	DM predictor of recurrent ischemic event
Repeat Revascularization	Zhang et al. (2023)	-	-	-	SHR for TyG index: 1.43 (p=0.002)

NGR: Normal Glucose Regulation; HR: Hazard Ratio; RR: Relative Risk; W: Women; M: Men; SHR: Subdistribution Hazard Ratio.

Predictive Power of Novel Biomarkers

A significant recent development has been the validation of simple, non-insulin-based surrogate markers for insulin resistance, which have shown remarkable prognostic value in the PCAD population (**Table 7**).

- **METS-IR & TyG Index:** The Metabolic Score for Insulin Resistance (METS-IR) and the Triglyceride-Glucose (TyG) index have been shown to be independent predictors of MACE in patients with PCAD . In a cohort of nearly 1,500 PCAD patients, a higher TyG index was strongly associated with a higher risk of MACE, with each standard deviation increase in the index conferring a 52% increase in risk . Similarly, the METS-IR was found to be a reliable predictor of MACE, with an AUC of 0.74 at 2 years, demonstrating good discriminatory power . These markers often outperform traditional risk factors and provide a cost-effective tool for enhanced risk stratification. The TyG index has also been specifically linked to the risk of recurrent revascularization in diabetic patients after PCI .
- **Inflammation and Mitochondrial Dysfunction:** The chronic low-grade inflammation central to both DM and atherosclerosis is reflected in biomarker profiles. High-sensitivity C-reactive protein (hs-CRP) levels are significantly higher in PCAD patients and are associated with recurrence risk . More novel research has identified markers of mitochondrial dysfunction, such as a lower mitochondrial DNA copy number (mtDNA-CN), as being significantly associated with EOCAD in patients who also have a higher prevalence of DM . This points to deeper cellular mechanisms through which metabolic stress accelerates vascular aging.

Table 7: Comparative Predictive Performance of Novel vs. Traditional Biomarkers for MACE in PCAD

Biomarker	Endpoint	Performance Metric (HR or OR [95% CI])
Diabetes Mellitus (vs. No DM)	All-Cause Mortality (15-yr)	Not reported, but 65% vs 24% mortality
	30-day Mortality after ACS	RR: 1.63 [1.41–1.89] (Men)
Prediabetes (vs. NGR)	All-Cause Mortality	HR: 1.17 [1.01–1.35]
	MACE	HR: 1.51 [1.05–2.18]
METS-IR (per SD increase)	MACE	HR: 1.41 [1.16–1.72]
TyG Index (per SD increase)	MACE	HR: 1.52 [1.27–1.82]
LPIR (Lipoprotein	Presence of CHD	6-fold increased risk vs. 40% for LDL-C

IR Score)	(Women <55)	
Current Smoking	CAD Recurrence	HR: 1.35 [1.13–1.61]

HR: Hazard Ratio; OR: Odds Ratio; RR: Relative Risk; MACE: Major Adverse Cardiovascular Events; NGR: Normal Glucose Regulation; SD: Standard Deviation.

DISCUSSION

Principal Findings: Diabetes as a Potent Accelerator of Premature Atherosclerosis

The collective evidence synthesized in this systematic review presents a clear and compelling conclusion: Diabetes Mellitus, along with its precursor state of insulin resistance, is a fundamental driver of Premature Coronary Artery Disease. The data consistently demonstrate that DM is not merely one risk factor among many but functions as a powerful disease accelerator. Its presence dramatically increases the prevalence of PCAD, dictates a more severe and diffuse anatomical presentation of coronary atherosclerosis, and portends a significantly worse long-term prognosis, which is characterized by markedly higher rates of mortality and major adverse cardiovascular events. The diabetic state appears to fundamentally alter the natural history of coronary disease, compressing decades of atherosclerotic development into a much shorter timeframe and leading to catastrophic clinical events in young adulthood. [7,8]

Unraveling the Pathophysiology: From Insulin Resistance to Plaque Rupture

The stark clinical and angiographic findings observed in PCAD patients with DM are the direct consequence of a complex and interconnected web of pathophysiological derangements. The process is initiated by **insulin resistance (IR)**, a state of suboptimal cellular response to insulin that is a hallmark of T2DM and metabolic syndrome . Initially, the pancreas compensates by producing

more insulin (compensatory hyperinsulinemia), but over time, pancreatic β-cell function declines, leading to overt **hyperglycemia** . [9.10]

Chronic hyperglycemia unleashes a torrent of vascular damage through multiple, synergistic pathways. First, it causes profound **endothelial dysfunction**, impairing the production of nitric oxide, a key vasodilator and anti-thrombotic molecule. This shifts the endothelial phenotype towards one that is vasoconstricted, pro-inflammatory, and pro-thrombotic . Second, excess glucose non-enzymatically binds to proteins and lipids, forming **Advanced Glycation End-products (AGEs)**. These AGEs accumulate in the vessel wall, cross-linking collagen to increase arterial stiffness. More perniciously, they interact with their receptor (RAGE) on inflammatory and endothelial cells, triggering a signaling cascade that perpetuates inflammation and oxidative stress . Third, hyperglycemia overwhelms mitochondrial function, leading to the overproduction of reactive oxygen species and a state of intense **oxidative stress**, which damages cellular components and further impairs endothelial function . Finally, these processes collectively fuel a **chronic, low-grade inflammatory state**. Adipose tissue in insulin-resistant individuals becomes dysfunctional, secreting pro-inflammatory cytokines like interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α), while the liver produces C-reactive protein (CRP) . [11,12,13]

This toxic metabolic milieu accelerates every stage of the atherosclerotic process. It promotes the infiltration of lipids into the arterial wall, facilitates the recruitment of inflammatory monocytes, and drives the transformation of these cells into foam cells, the building blocks of atherosclerotic plaque . The resulting plaques in younger patients are often more fibrotic with fewer necrotic or calcified components, but are paradoxically more unstable and prone to rupture—the direct trigger for an acute coronary syndrome at a tragically young age . This entire process functions as a self-amplifying, vicious cycle. Insulin resistance is a primary driver of inflammation and oxidative stress. In turn, systemic inflammation and oxidative stress can directly interfere with insulin signaling pathways and damage pancreatic β-cells, thereby worsening insulin resistance and hyperglycemia . This deleterious feedback loop creates an exponential, rather than linear,

progression of vascular damage. This explains the remarkable velocity of the atherosclerotic process observed in young individuals with T2DM and metabolic syndrome, culminating in clinical events decades earlier than in their metabolically healthy peers. [14,15,16]

Ethnic and Sex-Specific Considerations

The devastating impact of DM on PCAD is not uniformly distributed across all populations. There is compelling evidence for significant disparities based on ethnicity and sex.

South Asian Predisposition: Individuals of South Asian descent exhibit a markedly heightened susceptibility to both early-onset T2DM and PCAD . This "twin epidemic" is driven by a unique pathophysiology characterized by greater insulin resistance at a lower body mass index, limited adipose storage capacity, and a predisposition to hepatic fat accumulation . The incidence of T2DM is significantly higher and occurs 5 to 10 years earlier in South Asians compared to other ethnic groups, magnifying the lifetime exposure to the atherogenic diabetic state and accelerating the onset of CAD . [17,18,19]

Increased Vulnerability in Young Women: While CAD is traditionally more prevalent in men, the relative risk conferred by DM is substantially greater in women. Recent data show that the proportion of MIs attributable to patients <55 years old has increased, with the largest increases observed in young women . In women under 55, T2DM was associated with a tenfold greater risk of developing CHD, and factors like obesity and hypertension conferred a fourfold increased risk . This suggests that young women with metabolic dysfunction lose their relative protection from atherosclerosis and face a particularly aggressive disease course, a finding that underscores the need for targeted prevention strategies . [20,21]

Clinical Implications: A Paradigm Shift Towards Early and Aggressive Risk Stratification

The findings of this review carry profound and urgent implications for clinical practice. The remarkably high prevalence of previously undiagnosed diabetes and prediabetes at the time of a first

PCAD event represents a colossal failure of primary prevention and opportunistic screening . It signifies that for a large segment of the young adult population, the first indication of a severe underlying metabolic disorder is a life-threatening myocardial infarction. [22,23]

This reality necessitates a paradigm shift. The consistent and robust predictive power of simple, inexpensive, non-insulin-based biomarkers of IR, such as the **METS-IR and the TyG index**, is a critical finding . These tools can identify high-risk individuals long before their fasting glucose or HbA1c} meets the diagnostic criteria for diabetes, opening a crucial window for preventative intervention. Their incorporation into routine health screening for young adults, particularly those with central obesity, a family history of DM or PCAD, or other features of metabolic syndrome, should be strongly considered. [24,25]

Furthermore, the established concept of DM as a "CAD risk equivalent" must be applied with conviction and urgency in the young adult population . A diagnosis of T2DM in a person under 50 should no longer be viewed as an early-stage condition to be managed with diet and exercise alone. It must be recognized as a marker of advanced, albeit clinically silent, vascular disease. This diagnosis should trigger immediate, intensive, and multifactorial risk factor management on par with secondary prevention. This includes the initiation of high-intensity statin therapy, stringent blood pressure control to targets of <130/80 mmHg, and the preferential use of newer classes of antidiabetic agents (SGLT2 inhibitors and GLP-1 receptor agonists) that have demonstrated clear cardiovascular benefits, independent of their glucose-lowering effects. To hesitate in implementing such aggressive therapy is to ignore the overwhelming evidence that these young patients are on a rapid trajectory toward a premature cardiovascular event. [26,27]

Strengths and Limitations

The primary strength of this systematic review lies in its comprehensive and rigorous methodology. The search strategy was broad, and the review process adhered strictly to PRISMA guidelines. The use of the Newcastle-Ottawa Scale for quality appraisal ensures that the conclusions

are based on a methodologically sound body of evidence. The most significant strength is its novel, integrated synthesis, which connects the dots from molecular pathophysiology and advanced biomarkers to hard clinical outcomes, specifically within the understudied PCAD population. This provides a uniquely holistic perspective on the topic.

However, several limitations must be acknowledged. The principal limitation is the exclusive reliance on observational data (cohort and case-control studies). While such studies can establish strong, consistent associations, they cannot definitively prove causation due to the potential for residual confounding from unmeasured or unknown variables. Second, there was notable heterogeneity across the included studies in the precise age-based definitions of PCAD and, to a lesser extent, the diagnostic criteria for DM. This heterogeneity, while reflecting real-world clinical practice, can make direct comparisons between studies challenging. Finally, many of the included studies were conducted in specific geographic regions or ethnic groups (e.g., China, South Asia), which may limit the generalizability of some findings to other global populations, although the core associations appear to be consistent across diverse settings.

CONCLUSION AND RECOMMENDATIONS

Conclusion

In conclusion, this systematic review provides overwhelming and consistent evidence establishing Diabetes Mellitus as a critical determinant of the risk, angiographic severity, and adverse prognosis of Premature Coronary Artery Disease. The relationship is not merely correlational but is underpinned by a complex interplay of insulin resistance, chronic hyperglycemia, systemic inflammation, and endothelial dysfunction, which collectively create a hostile vascular environment and dramatically accelerate the atherosclerotic process. The presence of DM in a young individual effectively transforms CAD from a chronic, indolent disease of aging into an aggressive and often lethal condition of young adulthood. The findings underscore an urgent need to reframe our clinical approach to metabolic health in the young to stem the rising tide of

premature cardiovascular events.

Recommendations for Future Research and Clinical Practice

Based on the synthesis of evidence, the following recommendations are proposed:

For Clinical Practice:

1. **Implement Widespread Screening for Insulin Resistance:** Healthcare systems should advocate for the implementation of widespread, opportunistic screening for insulin resistance in young adults (ages 18-45), particularly those with established risk factors such as obesity (BMI >30 kg/m^2), a strong family history of PCAD or T2DM, or features of metabolic syndrome. This can be achieved using simple, cost-effective, non-fasting biomarkers like the TyG index or METS-IR, which can be calculated from a standard lipid panel and fasting glucose.
2. **Adopt Secondary Prevention-Level Care for Young Diabetics:** A diagnosis of T2DM in any individual under the age of 50 should immediately trigger a reclassification to the highest cardiovascular risk category. These patients should be managed with the same intensity as those with established ASCVD ("CAD risk equivalents"), including immediate initiation of high-intensity statin therapy, aggressive blood pressure control, and consideration of antidiabetic agents with proven cardiovascular benefits.

For Future Research:

1. **Prospective Validation of IR Biomarkers:** There is a need for large-scale, multi-ethnic, prospective cohort studies to validate the long-term predictive value of novel IR biomarkers (METS-IR, TyG index, LPIR) for the primary prevention of PCAD incidence in diverse populations.
2. **Early Intervention Trials:** Randomized controlled trials are urgently needed in young adults identified with prediabetes or early T2DM. These trials should test whether very early and

intensive interventions—combining lifestyle modification with aggressive pharmacological therapy (e.g., statins, SGLT2 inhibitors)—can halt or even regress the progression of subclinical atherosclerosis (as measured by imaging modalities like coronary artery calcium scoring or CT angiography) and ultimately prevent the onset of clinical PCAD.

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