

Factors Associated with Cardiovascular Risk Categories in Type 2 Diabetes Mellitus: Systematic Review

Fatores Associados às Categorias de Risco Cardiovascular em Diabetes Mellitus Tipo 2: Revisão Sistemática
Factores Asociados a las Categorías de Riesgo Cardiovascular en la Diabetes Mellitus Tipo 2: Revisión Sistemática

RESUMO

Objetivo: Investigar os fatores associados às diferentes categorias de risco cardiovascular em pessoas com diabetes mellitus tipo 2. **Método:** Revisão sistemática conduzida entre março e maio de 2025 nas bases PubMed, Web of Science e Embase. Foram incluídos estudos observacionais com adultos com diabetes mellitus tipo 2 e estratificação do risco cardiovascular em até dez anos. A qualidade metodológica foi avaliada pela Escala Newcastle-Ottawa. **Resultado:** Cinco estudos observacionais foram incluídos. Os principais fatores associados a maior risco cardiovascular foram hipertensão arterial, dislipidemia, controle glicêmico inadequado, obesidade, idade avançada e sexo masculino. Retinopatia diabética e níveis elevados de leptina também se associaram a maior risco. O uso de estatinas, especialmente em alta intensidade, apresentou efeito protetor. **Conclusão:** O risco cardiovascular no diabetes mellitus tipo 2 decorre da interação entre fatores modificáveis e não modificáveis, exigindo manejo integrado e investigação de determinantes sociais e comportamentais.

DESCRIPTORES: Diabetes mellitus; Doenças cardiovasculares; Fatores de risco; Revisão sistemática.

ABSTRACT

Objective: To investigate the factors associated with different categories of cardiovascular risk in individuals with type 2 diabetes mellitus. **Method:** A systematic review was conducted between March and May 2025 using the PubMed, Web of Science, and Embase databases. Observational studies involving adults with type 2 diabetes mellitus and cardiovascular risk stratification for up to ten years were included. Methodological quality was assessed using the Newcastle-Ottawa Scale. **Results:** Five observational studies were included. The main factors associated with higher cardiovascular risk were hypertension, dyslipidemia, poor glycemic control, obesity, older age, and male sex. Diabetic retinopathy and elevated leptin levels were also associated with increased cardiovascular risk. Statin use, particularly high-intensity statin therapy, showed a protective effect. **Conclusion:** Cardiovascular risk in type 2 diabetes mellitus results from the interaction of modifiable and non-modifiable factors, highlighting the need for integrated management and further investigation of social and behavioral determinants.

DESCRIPTORS: Diabetes mellitus; Cardiovascular diseases; Risk factors; Systematic Review.

RESUMEN

Objetivo: Investigar los factores asociados con las diferentes categorías de riesgo cardiovascular en personas con diabetes mellitus tipo 2. **Método:** Revisión sistemática realizada entre marzo y mayo de 2025 en las bases de datos PubMed, Web of Science y Embase. Se incluyeron estudios observacionales con adultos con diabetes mellitus tipo 2 y estratificación del riesgo cardiovascular a diez años. La calidad metodológica se evaluó mediante la Escala de Newcastle-Ottawa. **Resultados:** Se incluyeron cinco estudios observacionales. Los principales factores asociados con un mayor riesgo cardiovascular fueron la hipertensión arterial, la dislipidemia, el control glucémico inadecuado, la obesidad, la edad avanzada y el sexo masculino. La retinopatía diabética y los niveles elevados de leptina también se asociaron con un mayor riesgo cardiovascular. El uso de estatinas, especialmente de alta intensidad, mostró un efecto protector. **Conclusión:** El riesgo cardiovascular en la diabetes mellitus tipo 2 resulta de la interacción entre factores modificables y no modificables, lo que exige un manejo integral y una mayor investigación de los determinantes sociales y conductuales.

DESCRIPTORES: Diabetes mellitus; Enfermedades cardiovasculares; Factores de Riesgo; Revisión Sistemática.

Literature Review

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RECEIVED: 07/28/2026 APPROVED: 09/23/2026

How to cite this article: Campos CG, Barreto JC, Silva Silva AG, Escudeiro AF, Machado LSS, Santana LAS, Passinho RS. Factors Associated with Cardiovascular Risk Categories in Type 2 Diabetes Mellitus: Systematic Review. *Saúde Coletiva* (Brazilian Edition) [Internet]. 2026 [cited year month day];18 (113):20928-20945. Available from: DOI: 10.36489/saudecoletiva.2026v18i113p20928-20945



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INTRODUCTION

Type 2 diabetes mellitus (T2DM) is one of the leading chronic conditions associated with cardiovascular morbidity and mortality on a global scale, due to its high prevalence and close relationship with atherothrombotic outcomes.¹ Among the most significant complications are coronary artery disease, cerebrovascular disease, and peripheral artery disease, all of which contribute significantly to the clinical and healthcare burden of this population.²

Cardiovascular risk stratification in people with type 2 diabetes results from the interaction between modifiable and nonmodifiable factors, including hypertension, dyslipidemia, obesity, physical inactivity, advanced age, male sex, and socioeconomic determinants. These components exert an additive and, of-

ten, synergistic effect, accelerating the progression of atherosclerosis and worsening the cardiovascular prognosis.^{3,4}

In this context, hypertension and dyslipidemia remain central risk determinants, especially when associated with insulin resistance and visceral adiposity. Obesity, in turn, promotes chronic inflammation, endothelial dysfunction, and metabolic instability, while a sedentary lifestyle exacerbates these pathogenic mechanisms.^{3,5}

Cardiovascular risk assessment can be performed using clinical criteria and predictive tools that integrate laboratory, hemodynamic, and epidemiological variables.⁶ Early identification of individuals at higher risk is essential for targeting intensive, multifactorial interventions, including blood pressure control, lipid management, glycemic optimization, and lifestyle modification.^{7,8}

In addition to traditional risk factors,

inadequate glycemic control, smoking, alcohol consumption, and markers of microangiopathy—such as diabetic retinopathy—have also been associated with a worse cardiovascular prognosis in individuals with type 2 diabetes.⁹

In light of this, this systematic review aimed to investigate the factors associated with different categories of cardiovascular risk in people with type 2 diabetes mellitus.

METHOD

Eligibility Criteria

This systematic review included primary observational epidemiological studies, with no restrictions regarding year of publication or language, that investigated individuals with type 2 diabetes mellitus exposed to one or more factors associated with cardiovascular risk, as well as studies that presented



a cardiovascular risk stratification into low, intermediate, high, or very high for an estimated ten-year period.

Studies were considered eligible if their population consisted of adults over 18 years of age diagnosed with type 2 diabetes mellitus, provided they included an assessment or classification of 10-year cardiovascular risk using tools recognized in the scientific literature.

Studies that included participants with pre-existing cardiovascular disease were excluded, due to the influence of this condition on the estimation of future cardiovascular risk.

Information Sources

The search was conducted in the following health databases: *Medical Literature Analysis and Retrieval System Online (MEDLINE/PubMed via the National Library of Medicine)*, *Web of Science (WoS)*, and *Excerpta Medica Database (EMBASE)*.

Search strategy

The strategy was structured based on the PECO acronym (Population, Exposure, Comparator, and Outcome), ensuring the inclusion of all elements relevant to the focus of the review. The research question for this review was: What is the association between lifestyle factors, biological variables, and social determinants and cardiovascular risk in people with type 2 diabetes mellitus? In this case, P represents people with type 2 diabetes mellitus; E encompasses factors associated with cardiovascular risk, such as variables related to lifestyle habits, biological factors, and social factors; C (Comparator) does not apply; and O refers to cardiovascular risk. The search included controlled terms, such as MeSH (*Medical Subject Headings*) descriptors in PubMed and WoS and Emtree in EMBASE, as well as free-text terms. Keywords and descriptors were combined using Boolean operators ("AND" and "OR") to increase the sensitivity and specificity of the search (Table 1). The terms and

synonyms were adapted for each database, taking into account their specific characteristics. No restrictions were applied regarding language or year of publication, allowing for the inclusion

of studies published up to the search completion date. Access was provided through the institutional infrastructure (CAPES journal portal with CAFE authentication).

Table 1 – Search strategy for the systematic review. Teixeira de Freitas, Bahia, Brazil. 2025.

Search Strategies	Author(s)
PubMed	("Diabetes Mellitus, Type 2"[MeSH] OR "Type 2 Diabetes Mellitus" OR "T2DM") AND ("Adults"[MeSH] OR "Adult" OR "18 years and older") AND ("Socioeconomic Factors"[MeSH] OR "Socioeconomic Status" OR "Income" OR "Education" OR "Inflammatory Markers"[MeSH] OR "C-Reactive Protein" OR "Interleukins" OR "Blood Glucose"[MeSH] OR "Glucose" OR "Hemoglobin A1c"[MeSH] OR "Glycated Hemoglobin" OR "Blood Lipids"[MeSH] OR "Cholesterol" OR "Triglycerides" OR "Race"[MeSH] OR "Ethnicity" OR "Skin Color" OR "Residence Characteristics"[MeSH] OR "Urban" OR "Rural" OR "Age Factors"[MeSH] OR "Age" OR "Elderly" OR "Sex Factors"[MeSH] OR "Gender" OR "Male" OR "Female" OR "Hypertension"[MeSH] OR "High Blood Pressure" OR "Polycystic Ovary Syndrome"[MeSH] OR "PCOS" OR "Sleep Apnea Syndromes"[MeSH] OR "Obstructive Sleep Apnea" OR "Obesity"[MeSH] OR "Overweight" OR "Smoking"[MeSH] OR "Tobacco Use" OR "Alcohol Drinking"[MeSH] OR "Alcohol Abuse" OR "Substance-Related Disorders"[MeSH] OR "Drug Abuse" OR "Self Medication" Aplicado filtro: observacional study.
WoS	TS=("Diabetes Mellitus, Type 2" OR "T2DM" OR "Type 2 Diabetes" OR "Diabetes Mellitus" OR "Adult-Onset Diabetes" OR "Metabolic Disorder") AND TS=("Cardiovascular Risk" OR "Heart Disease" OR "Cardiovascular Health" OR "Cardiovascular Events" OR "Atherosclerosis" OR "Myocardial Infarction" OR "Stroke" OR "Coronary Artery Disease") AND TS=("Lifestyle Factors" OR "Diet" OR "Healthy Eating" OR "Nutrition" OR "Physical Activity" OR "Exercise" OR "Sedentary Behavior" OR "Smoking" OR "Alcohol Use" OR "Substance Use") AND TS=("Biological Factors" OR "Hypertension" OR "High Blood Pressure" OR "Obesity" OR "Dyslipidemias" OR "Inflammation" OR "C-Reactive Protein" OR "Interleukins" OR "Blood Pressure" OR "Glucose Levels" OR "Metabolic Syndrome" OR "Insulin Resistance") AND TS=("Social Determinants" OR "Socioeconomic Status" OR "Income" OR "Education" OR "Race" OR "Ethnicity" OR "Health Disparities" OR "Access to Healthcare" OR "Neighborhood Characteristics") AND TS=("Epidemiological Studies" OR "Cross-Sectional Studies" OR "Cohort Studies" OR "Longitudinal Studies" OR "Observational Studies" OR "Case-Control Studies" OR "Population-Based Studies")
EMBASE	('type 2 diabetes mellitus'/exp OR 't2dm') AND ('adult'/exp OR '18 years and older') AND ('socioeconomic factors'/exp OR 'education' OR 'income' OR 'race'/exp OR 'ethnicity') AND ('biomarker'/exp OR 'hba1c' OR 'c-reactive protein' OR 'ldl cholesterol' OR 'waist hip ratio') AND ('comorbidity'/exp OR 'hypertension' OR 'obesity' OR 'dyslipidemia' OR 'subclinical inflammation') AND ('study design'/exp OR 'cross-sectional' OR 'cohort' OR 'case control')

Source: Prepared by the authors.

Selection process

The study selection process was conducted in two main stages: initial screening and detailed evaluation. The initial screening involved reviewing the titles and abstracts of the retrieved studies and was performed by two independent reviewers, who

applied the previously defined eligibility criteria.

To identify potential duplicates, the *Rayyan – Intelligent Systematic Review* software was used, ensuring a rigorous approach to identifying relevant studies. Disagreements during the selection process were resolved by consensus among the reviewers or,

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when necessary, by a third evaluator.

The initial screening was followed by a full reading of the full-text articles of potentially eligible studies, using a structured checklist to assess adherence to the inclusion and exclusion criteria. The reasons for excluding studies at this stage were recorded in an exclusion table. The process of identifying, screening, and including articles in the review was detailed using the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) flowchart.

Data Collection Process

Data extraction was performed using a standardized spreadsheet developed in *Microsoft Excel*, containing the following fields: author(s), year and location of the study, population characteristics, exposure variables (cardiovascular risk factors), outcomes (cardiovascular risk categories: low, intermediate, high, or very high), statistical analysis used, measures of association (odds ratio, relative risk, *hazard ratio*), and 95% confidence intervals. The extracted data were stored in a centralized database, and regular *backups* were performed to ensure data security.

Data Items

The data items extracted from the studies included variables related to biological, behavioral, and socioeconomic factors associated with cardiovascular risk in individuals with type 2 diabetes mellitus. Among the biological factors, the following stood out: hypertension, dyslipidemia, obesity, glycated hemoglobin (HbA1c) levels, LDL cholesterol, C-reactive protein, and waist-to-hip ratio. Behavioral factors included smoking, physical inactivity, dietary patterns, physical activity, and alcohol consumption. Socioeconomic factors included income, educational attainment, and access to health care services. Information was also collected

regarding the cardiovascular risk categories used in each study, classified as low, intermediate, high, and very high risk for cardiovascular events over a 10-year period.

In addition, methodological data were extracted from the studies, including authors, year of publication, country of origin, study design, population characteristics, sample size, instruments used to assess cardiovascular risk, variables analyzed, statistical methods employed, and the main outcomes investigated. The data were organized into a standardized spreadsheet, previously developed by the researchers, to ensure uniformity, traceability, and reliability in the process of extracting and synthesizing the information.

Assessment of Risk of Bias in the Studies

The assessment of risk of bias in the included studies was a fundamental step in ensuring the validity and reliability of the conclusions of this systematic review. This process allowed for the identification of potential sources of methodological bias that could influence the interpretation of the results. The *Newcastle-Ottawa Scale* (NOS) was used for observational studies.¹⁰ It assessed aspects such as participant selection, measurement of exposure and outcomes, and control for confounding factors. The assessment was conducted independently by two reviewers to minimize potential biases in the analysis. Any disagreements were resolved by consensus or, when necessary, with the intervention of a third reviewer.

Effect Measures

The effect measures considered for the synthesis of the included studies comprised the *hazard ratio* (HR) and *odds ratio* (OR), along with their respective 95% confidence intervals (95% CI), as reported in the original studies. These measures were used to

estimate the magnitude of the association between clinical, metabolic, behavioral, and sociodemographic factors and the different categories of cardiovascular risk in individuals with type 2 diabetes mellitus. In studies that used multivariate models, the effect measures were derived primarily from Cox regression and logistic regression. In contrast, studies that performed descriptive or bivariate analyses presented their findings according to the statistical methods adopted by the authors, without standardizing comparable measures.

Methods of Synthesis

The synthesis of the included studies was conducted in a narrative and descriptive manner, taking into account the methodological, clinical, and epidemiological characteristics of the selected studies. The data were organized into a summary table containing information on the authors, year of publication, study location, mean age of the study population, sex, factors associated with cardiovascular risk, statistical analysis methods, effect measures used, estimate values, 95% confidence intervals, risk of bias classification, and the cardiovascular risk category identified in each study.

Subsequently, the studies were grouped according to factors associated with cardiovascular risk in individuals with type 2 diabetes mellitus, including biological, clinical, and behavioral variables. The reported effect measures, including *hazard ratio* (HR) and *odds ratio* (OR), along with their respective 95% confidence intervals, were described and compared qualitatively, taking into account the methodological characteristics of each study.

No meta-analysis was performed due to the small number of included studies and the high methodological heterogeneity observed among them, particularly regarding study designs, statistical methods used, variables

analyzed, cardiovascular risk stratification tools, and reported effect measures. Furthermore, some of the studies presented only descriptive or bivariate analyses, without comparable estimates, which made it impossible to quantitatively combine the results in a statistically robust and methodologically appropriate manner.

Assessment of the certainty of the evidence

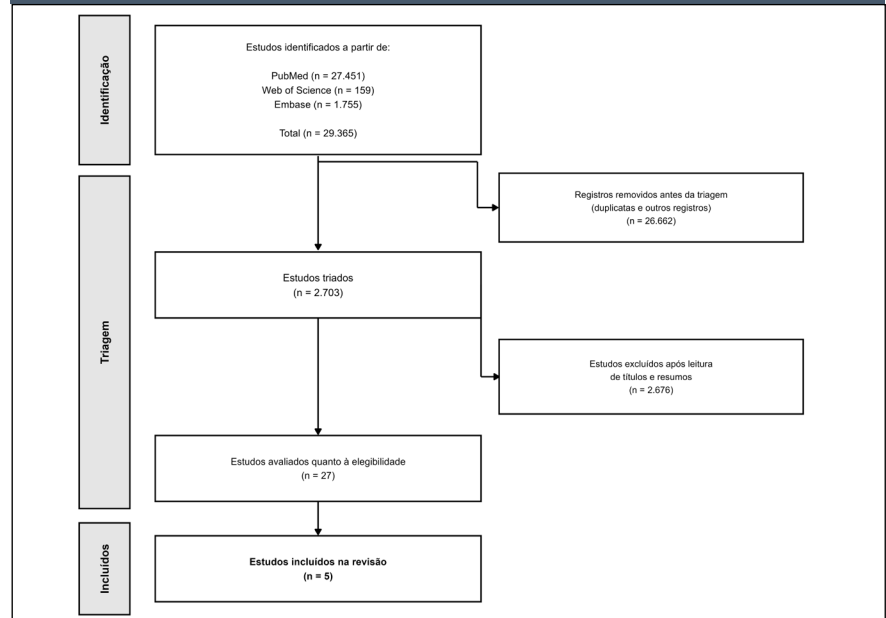
The methodological quality of the included observational studies was assessed using the Newcastle-Ottawa Scale (NOS)¹⁰, a widely used tool for analyzing participant selection, comparability between groups, and assessment of outcomes or exposures. Studies with a score of seven points or higher were classified as having a low risk of bias.

RESULTS

Study selection

The database search strategy identified 29,365 records: 27,451 from *PubMed*, 1,755 from *Embase*, and 159 from *Web of Science*. After removing studies excluded during the initial screening and duplicates, 2,703 remained for screening by titles and abstracts, of which 2,676 were excluded for failing to meet the eligibility criteria. Twenty-seven studies proceeded to full-text review; those without free access to the full text ($n=2$), with only partial content ($n=5$), or without cardiovascular risk classification according to the defined criteria ($n=14$) were excluded. In the end, five studies met all criteria and formed the basis of the qualitative synthesis of this systematic review. The complete process of study identification, screening, eligibility assessment, and inclusion is presented in Figure 1.

Figure 1 – Flowchart of the process of identification, screening, eligibility, and inclusion of studies, Teixeira de Freitas, Bahia, Brazil, 2026.



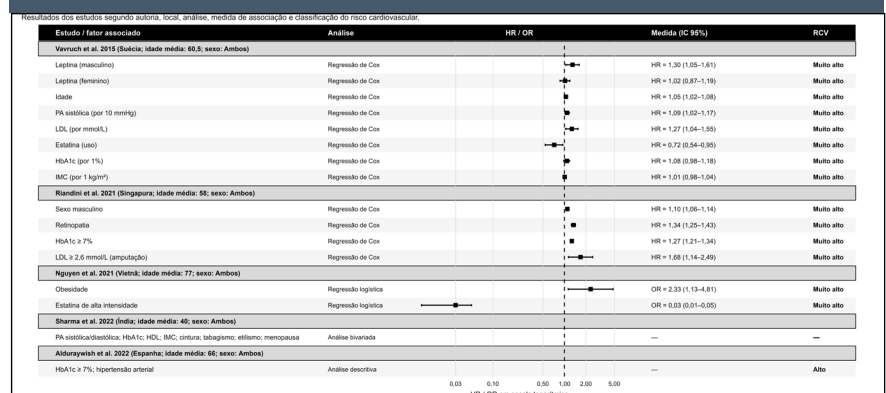
Fonte: Elaborado pelos autores (2026), com base nas recomendações do PRISMA.

Study characteristics

This systematic review included five observational studies conducted in Sweden, Singapore, Vietnam, India, and Spain, published between 2015 and 2022. The study populations included adults of both sexes, with a mean age ranging from 40 to 77 years. Most studies employed multivariate analyses (Cox and logistic regression) to

assess the association between clinical, metabolic, and behavioral factors and cardiovascular risk in type 2 diabetes. Two studies used only descriptive and bivariate analyses. The main factors investigated included hypertension, glycated hemoglobin, obesity, lipid profile, smoking, menopause, retinopathy, body mass index, and statin use (Figure 2).

Figure 2 – Factors associated with cardiovascular risk in type 2 diabetes mellitus, Teixeira de Freitas, Bahia, Brazil, 2026.



Source: Prepared by the authors (2026), based on the included studies. CVR = cardiovascular risk; HR = hazard ratio; OR = odds ratio; 95% CI = 95% confidence interval.

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The risk of bias in the included studies was assessed using the *Newcastle-Ottawa Scale* (NOS)¹⁰, considering the domains of selection, comparability, and outcome/exposure. All studies scored between eight and nine points and were classified as having a low risk of bias. Two studies—Vavrch *et al.*¹¹, Riandini *et al.*¹² and Alduraywish *et al.*¹³ achieved the maximum score on the scale, while two others—Nguyen *et al.*⁸ and Sharma *et al.*⁽¹⁴⁾—had minor limitations related to the comparability and outcome/exposure assessment criteria. Overall, the studies demonstrated adequate methodological quality to be included in the review synthesis.

Results of the Individual Studies

The included studies identified various factors associated with cardiovascular risk in type 2 diabetes (T2D). The most common biological and clinical factors were advanced age, male sex, hypertension, elevated glycated hemoglobin, dyslipidemia, obesity, retinopathy, and elevated systolic blood pressure. Behavioral variables, such as smoking and alcohol consumption, were also investigated. Regarding effect measures, three studies presented quantitative estimates (HR or OR) with 95% confidence intervals, while two studies were limited to descriptive or bivariate analyses, without adjusted measures of association.

Results of the Syntheses

The qualitative synthesis revealed an association between multiple clinical, metabolic, and behavioral factors and an increased cardiovascular risk in type 2 diabetes (T2D). Modifiable factors predominated: glycemic control, blood pressure, lipid profile, and obesity, in addition to non-modifiable factors such as age and sex. A meta-analysis was not feasible due to the small number

of studies and high methodological heterogeneity regarding study designs, risk stratification tools, variables, statistical methods, and effect sizes. Only three studies presented comparable effect sizes, limiting a robust quantitative synthesis.

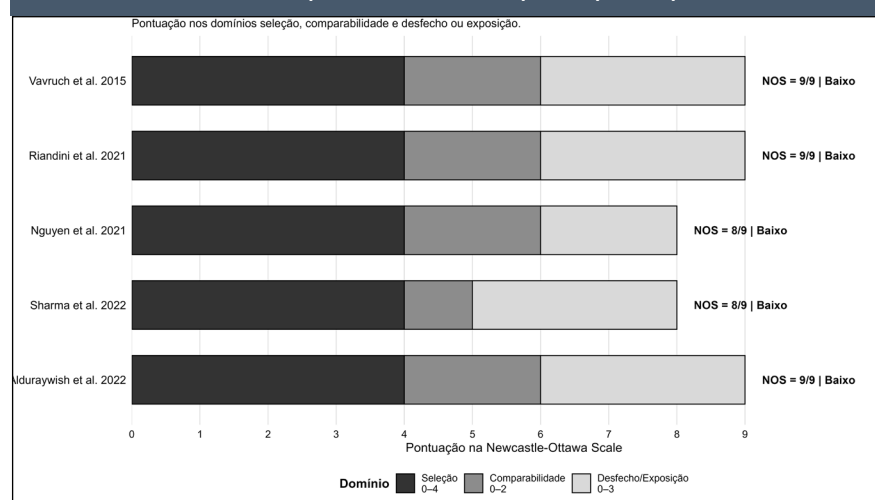
Publication bias

It was not possible to conduct a formal assessment of publication bias—such as a visual inspection of a funnel plot or statistical tests—due to the small number of studies, broad search strategies, and strict application of predefined eligibility criteria.

Certainty of the evidence

The certainty of the evidence was assessed narratively, considering methodological quality, consistency of findings, precision of estimates, and heterogeneity among studies. Although the studies showed a low risk of bias according to the *Newcastle-Ottawa Scale*, the predominance of observational designs, the small number of studies, and methodological diversity limited the robustness of the available evidence (Figure 3).

Figure 3 – Assessment of the risk of bias of the included studies using the Newcastle-Ottawa Scale, Teixeira de Freitas, Bahia, Brazil, 2026.



Source: Prepared by the authors (2026), based on the assessment of the included studies. NOS = Newcastle-Ottawa Scale. Selection: 0–4 points; comparability: 0–2 points; outcome/exposure: 0–3 points.

DISCUSSION

This systematic review, based on five observational studies conducted between 2015 and 2022, showed that hypertension, dyslipidemia, inadequate glycemic control, obesity, advanced age, and male sex are consistently associated with higher categories of cardiovascular risk in individuals with type 2 diabetes mellitus; furthermore, diabetic retinopathy and elevated serum leptin levels suggest prognostic value, while statin use—particularly at high

doses—demonstrated a protective effect, reinforcing the multifactorial and synergistic nature of cardiovascular risk in this population.^{15,16}

Hypertension and elevated systolic blood pressure have been consistently associated with an increased cardiovascular risk in individuals with type 2 diabetes (T2D). In Vavrch *et al.*¹¹, each 10 mmHg increase in systolic blood pressure was associated with an increased risk of ischemic heart disease, while Alduraywish *et al.*¹³ identified hypertension as a variable associated

with the high cardiovascular risk category.

The 2021 guidelines from the *American Diabetes Association* (ADA) highlight hypertension as a key modifiable factor in the cardiometabolic management of type 2 diabetes, recommending its strict control; in the context of CKM syndrome, its relevance stems from its interaction with insulin resistance, chronic inflammation, and renal dysfunction, which justifies an early and integrated approach to reducing overall cardiovascular risk.^{15,16} Dyslipidemia, particularly elevated LDL cholesterol, has also been consistently associated consistently with an increased cardiovascular risk, with a 1 mmol/L increase linked to a higher risk of ischemic heart disease and LDL ≥ 2.6 mmol/L associated with a higher risk of lower limb amputation, highlighting both coronary and peripheral vascular impacts.^{11,12}

Peripheral arterial disease and chronic venous insufficiency represent significant vascular manifestations in individuals with type 2 diabetes, which are often underestimated in clinical practice and associated with a higher burden of cardiovascular morbidity and mortality.^{11,18} In this context, the 2022 *ADA/European Association for the Study of Diabetes* (EASD) consensus recommends prioritizing lipid-lowering therapy with statins in high-risk patients, with individualized LDL targets based on cardiovascular profile.¹⁹

Inadequate glycemic control, especially HbA1c $\geq 7\%$, was associated with increased cardiovascular risk in two studies, in relation to lower extremity complications and high-risk classification.^{12,13} Although Vavrukh *et al.*¹¹ did not observe a statistically significant association in the multivariate model, the body of findings reinforces the relevance of chronic hyperglycemia in cardiovascular risk stratification in type 2 diabetes.

Inadequate self-care, including irregular eating habits and poor adher-

ence to glycemic monitoring, is associated with poorer glycemic control and increased cardiovascular risk in individuals with type 2 diabetes.²⁰ Accordingly, the 2022 ADA and EASD consensus recommends individualized glycemic targets based on cardiovascular risk profile and patient preferences, with a priority on cardioprotective medications for individuals at higher risk.¹⁹ Studies in primary care also show that a significant proportion of patients do not simultaneously achieve glycemic, blood pressure, and lipid targets, highlighting the complexity of multifactorial management.²¹

Obesity was associated with the very high cardiovascular risk category in individuals with type 2 diabetes (OR: 2.33; 95% CI: 1.13–4.81),⁸ with body mass index and waist circumference ranking among the associated variables in the bivariate analysis.¹⁴ Its pathophysiological role stems from visceral obesity, which promotes insulin resistance, low-grade chronic inflammation, and endothelial dysfunction—key links between type 2 diabetes and major cardiovascular events.¹⁵ Leptin, secreted by adipose tissue in proportion to fat mass, was identified as an independent factor associated with ischemic heart disease in men with T2D (HR: 1.30; 95% CI: 1.05–1.61), an association not replicated in women (HR: 1.02; 95% CI: 0.87–1.19).¹¹ This finding suggests that leptin may act as a sex-specific biomarker of cardiometabolic dysfunction, expanding the possibilities for risk stratification beyond conventional anthropometric indicators.¹¹

The clinical utility of cardiac biomarkers in this population was corroborated by a study that demonstrated the relevance of NT-proBNP in identifying subclinical cardiac impairment in outpatients with type 2 diabetes, even in the absence of obvious symptoms of heart failure, thereby supporting risk stratification in both primary and specialized care.²²

Advanced age and male sex were consistently associated with an increased cardiovascular risk. In the adjusted analysis of one of the included studies, each one-year increase in age was associated with an increased risk of ischemic heart disease (HR: 1.05; 95% CI: 1.02–1.08),¹¹ while male sex was an independent risk factor for lower-limb complications (HR: 1.10; 95% CI: 1.06–1.14).¹² In the context of type 2 diabetes (T2D), aging is associated with the progressive accumulation of vascular damage, reduced renal function, and a higher prevalence of comorbidities—conditions that, together, synergistically increase overall cardiovascular risk.¹³

Corroborating these findings, the Portuguese observational study PIC-T2RE confirmed a high prevalence of established cardiovascular disease and accumulated risk factors in patients with type 2 diabetes (T2D) followed in a hospital setting, with a predominance of older individuals and males in the highest-risk categories.²³ These data align with the results of the present review and reinforce the need for screening and early intervention strategies in these subpopulations.

Diabetic retinopathy was identified as a factor associated with an increased risk of lower extremity complications (HR: 1.34; 95% CI: 1.25–1.43).¹² Clinically, its relevance stems from the fact that retinopathy reflects systemic microangiopathy and may signal vascular impairment in multiple territories, including the coronary and peripheral systems. The coexistence of retinopathy with other microvascular complications—peripheral neuropathy and nephropathy—amplifies cardiovascular risk by reflecting prolonged exposure to hyperglycemia and deleterious hemodynamic factors.^{12,15} A narrative review on preventable hospitalizations in type 2 diabetes highlighted that patients with established microvascular complications are at higher risk of hospitalizations due to preventable

cardiovascular causes, reinforcing the need for early identification and management of these conditions as part of comprehensive care.²⁴

Statin use was the main protective factor identified in this review. A 28% reduction in the risk of ischemic heart disease was observed among patients with type 2 diabetes who were taking statins (HR: 0.72; 95% CI: 0.54–0.95)¹¹, and the use of high-intensity statins was associated with a significant reduction in the likelihood of being classified as being at very high cardiovascular risk (OR: 0.03; 95% CI: 0.01–0.05)⁸. These findings are consistent with the recommendations of major international guidelines, which indicate moderate- to high-intensity statins as first-line therapy for reducing cardiovascular risk in patients with type 2 diabetes at high and very high risk.¹⁶

From the perspective of pharmacological management, metformin remains an essential drug in the treatment of type 2 diabetes, with well-established evidence of metabolic benefit and a reaffirmed role in the management of patients with cardiorenometabolic conditions.²⁵ Sodium-glucose cotransporter 2 (SGLT2) inhibitors provide additional cardiovascular and renal protection, with demonstrated benefits regardless of glycemic control in high-risk patients with T2DM,

including those with chronic kidney disease. The ADA/EASD consensus (2022) and the ADA guidelines (2021) recommend incorporating agents with cardioprotective benefits—such as SGLT2 inhibitors and GLP-1 receptor agonists—into the treatment regimen for patients with type 2 diabetes and high cardiovascular risk, regardless of HbA1c levels, thereby reinforcing an approach centered on risk rather than glycemic control alone.^{16,19}

This review has methodological limitations. The small number of studies (n=5) and the heterogeneity among study designs, risk assessment tools, variables, and statistical methods made a meta-analysis unfeasible. Two studies were limited to descriptive or bivariate analyses, without adjusted estimates, compromising comparability. The geographic diversity (Sweden, Singapore, Vietnam, India, and Saudi Arabia) enhances representativeness but requires caution when extrapolating to Brazil, given the differences in epidemiology, socioeconomic status, and access to healthcare. Finally, the absence of studies on socioeconomic determinants and nonpharmacological interventions is a significant gap, given that income, education, and access to care modulate cardiovascular outcomes in type 2 diabetes.^{13,24}

The protocol for this review was previously registered on the *Open Sci-*

ence Framework (OSF) platform, ensuring transparency and methodological traceability. The registration is available under the DOI: <https://doi.org/10.17605/OSF.IO/NXPR4>.

CONCLUSION

This study demonstrated that cardiovascular risk in individuals with type 2 diabetes mellitus is determined by a combination of modifiable and non-modifiable factors, notably advanced age, male sex, hypertension, elevated LDL, HbA1c

≥ 7%, and obesity. Additional markers, such as diabetic retinopathy and elevated leptin, suggest potential prognostic value in cardiovascular risk stratification. In contrast, the use of statins, especially at high doses, showed a consistent protective effect.

The findings underscore the need for an early, individualized, and multifactorial clinical approach, with a focus on blood pressure, lipid, and glycemic control, as well as the management of excess weight. The methodological limitations of the included studies, combined with the heterogeneity among the investigations, point to the need for more robust longitudinal studies that incorporate social determinants and biomarkers to improve the prediction and prevention of cardiovascular risk in this population.

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Funding

None.

Conflict of Interest Statement and Data Availability Statement

Conflict of interest: The authors declare that there is no conflict of interest.

Data availability: The data supporting the findings of this study are available upon request from the corresponding author.