META-ANALYSIS *Volume 15 (Issue 2), 2026*

PAKISTAN JOURNAL OF MEDICINE & DENTISTRY

Evaluating the Schematic Assessment of Impact of Glycaemic Control on Cardiac Autonomic Neuropathy in Patients with Type 2 Diabetes Mellitus

Uday Shree Akkala Shetty1, Muhammad Zaman Baloch2, Mustafa Duraab Kalwar3, Kainat Zafar[4]

[1]*Department of Internal Medicine, Southern Regional Medical Center, Riverdale, Georgia, USA,* [2]*Department of Cardiology, Indus Medical College, The University of Modern Science, Tando Muhammad Khan,* [3]*Department of Biological Sciences, Karachi Grammar School, Karachi,* [4]*Department of Pathology, Akhtar Saeed Medical College, Akhtar Saeed Hospital, Lahore, Pakistan.*

ABSTRACT

Background: Cardiac autonomic neuropathy (CAN) is a severe, poorly known complication of type 2 diabetes mellitus (T2DM), which is the loss of autonomic control of heart rate and blood pressure and is linked to morbidity and mortality. This meta-analysis and systematic review aimed to determine the effect of interventional measures on the cardiac autonomic function of patients with type 2 diabetes mellitus (T2DM).

Methods: An extensive search in PubMed, Scopus, Web of Science, and Google Scholar until November 2025 was conducted. The randomized controlled trials, the prospective cohort studies, and the observational studies that measure cardiac autonomic functioning in patients with T2DM were covered. Risk of bias of the included observational and interventional studies was assessed using the Newcastle–Ottawa Scale (NOS) for cohort and cross-sectional studies, and the Cochrane ROB tool for randomized trials; and the degree of certainty of evidence was gauged through the GRADE method.

Results: 12 studies passed the inclusion criteria. The meta-analysis of both primary outcomes; E: I ratio and Valsalva ratio showed no statistically significant improvements, respectively. There was a high heterogeneity (I^2 = 95-98%), which could probably be explained by the variation in the nature of patients, types of interventions, and protocols of measurement. The rigor of findings was ensured by subgroup and sensitivity analysis.

Conclusion: T2DM patients have mixed effects on cardiac autonomic functioning in terms of interventions. Non-pharmacological and multimodal approaches have the potential to be of value, particularly in optimal glycaemic control, yet standardized trials are needed to offer certain directions.

Keywords: Diabetic Neuropathies, Diabetes Mellitus Type 2, Valsalva Maneuvers, Heart Rate, Glycaemic Control, Percutaneous Coronary Intervention.

***Corresponding Author: Kainat Zafar**
Email: kainatzafarpatho@gmail.com

How to cite: Shetty USA, Baloch MZ, Kalwar MD, Zafar K. Evaluating the Schematic Assessment of Impact of Glycaemic Control on Cardiac Autonomic Neuropathy in Patients with Type 2 Diabetes Mellitus, A Systematic Review and Meta-Analysis. Pak J Med Dent. 2026 April ;15(2): 361-380. Doi: https://doi.org/10.36283/ziun-pjmd15-2/030.

Received: Wed, November 26, 2026 **Accepted:** Fri, April 10, 2026 **Published:** Mon, April 13, 2026

INTRODUCTION

Cardiac autonomic neuropathy (CAN) is a severe, poorly known complication of type 2 diabetes mellitus (T2DM), which is the loss of autonomic control of heart rate and blood pressure [1]. It is linked to morbidity and mortality because of arrhythmias, asymptomatic myocardial ischemia, and cardiac death [2]. The most common noninvasive measures that can be used to assess autonomic performance and therefore the degree of sympathetic and parasympathetic balance are heart rate variability (HRV) and cardiovascular reflex tests such as the E: I ratio and Valsalva ratio [3].

Early diagnosis of CAN is essential, since autonomic dysfunction is most times silent and can be diagnosed at a later stage. Autonomic impairment is caused by a number of factors, with poor glycaemic control, prolonged duration of disease, hypertension, dyslipidemia, and diabetic complications such as nephropathy and peripheral neuropathy being among them [4]. Long-term monitoring of autonomic functioning, identification of high-risk individuals, and timely interventions are the features of the noninvasive methods such as the analysis of HRV and cardiovascular reflexes that enable clinicians to improve cardiovascular outcomes and decrease mortality among T2DM populations [5,6].

Autonomic dysfunction is markedly observed in T2DM patients, especially those who have poor glycaemic control or have had the disease over a long period of time, with T2DM patients experiencing slowed HRV, impaired reflex responses, and baroreceptor sensitivity [7]. The comorbidities of this dysfunction include diabetic kidney disease, peripheral neuropathy, and chronic coronary syndromes, which only make the cardiovascular regulation worse. Early diagnosis and treatment of CAN are highly essential to decrease cardiovascular risks and enhance long-term outcomes of T2DM populations [8,9].

The interventional measures to normalize autonomic functioning involve pharmacological treatment options, ideal glycaemic regulation, Revascularization therapy, such as percutaneous coronary intervention (PCI), and non-pharmacological treatment, such as slow deep breathing (SDB) training [10,11]. These interventions have been demonstrated to alter HRV parameters and to enhance parasympathetic tone, but the extent and variability of the effects of such interventions are found to differ among studies because of patient groups, disease severity, and study designs [11].

Although the research is increasing, current evidence is mixed regarding the efficacy of interventions in enhancing of E: I ratio, Valsalva ratio, and overall cardiac autonomic functioning in T2DM. The difference in the study design, sample size, type of intervention, follow-up, and time of assessment are among the factors that lead to inconsistent results. An organized review is required to bring together available evidence, to measure the total impact of the interventions, and to guide the clinician and researchers to treat CAN in patients with T2DM [12].

This meta-analysis and systematic review aimed to determine the effect of interventional measures on the cardiac autonomic function of patients with type 2 diabetes mellitus (T2DM). It assessed the impact of an interventional approach on cardiac autonomic function in diabetic patients with T2DM, considering the E: I ratio, Valsalva ratio, and HRV parameters. The secondary goals were to determine the quality of the study, risk of bias, and heterogeneity of findings to make clinical inferences and guide future research.

METHODS

This systematic review and a meta-analysis followed PRISMA 2020 guidelines [13].

PubMed, Scopus, Web of Science, and Google Scholar were searched in November 2025. The search terms were MeSH terms, as well as free-text words, that is, cardiac autonomic neuropathy, heart rate variability, E: I ratio, Valsalva ratio, type 2 diabetes mellitus, T2DM, percutaneous coronary intervention, and Boolean operators (AND, OR). Manual screening of reference lists of sampled studies was also carried out to further screen more qualified articles.

One sample search query was:

(("cardiac autonomic neuropathy" OR "CAN" OR "autonomic dysfunction") AND ("type 2 diabetes mellitus" OR "T2DM") AND ("heart rate variability" OR "HRV" OR "E:I ratio" OR "Valsalva ratio") AND ("intervention" OR "revascularization" OR "slow deep breathing" OR "SDB" OR "training" OR "treatment")).

The inclusion criteria included: randomized controlled trials or prospective/observational studies on cardiac autonomic function of T2DM patients where quantitative data of E: I ratio, and Valsalva ratio, were reported with extractable means, SDs, and sample sizes.

Articles were not included in the research that were case reports, reviews, editorials, animal studies, in vitro studies, or that did not provide extractable numerical data.

Two reviewers were involved in screening titles, abstracts, and full texts, and a third reviewer overruled any disagreement. The data extraction form was a standardized form that was used to gather: author, year, study design, population size, type of intervention, comparator, measured autonomic parameters, and follow-up period. In the cases when it was required, authors were contacted to find missing data.

The primary outcomes of this meta-analysis were the E: I ratio and the Valsalva ratio. Quantitative analyses were only done with studies that could extract means, SDs, and sample sizes.

Risk of bias of the included observational and interventional studies was assessed using the Newcastle–Ottawa Scale (NOS) for cohort and cross-sectional studies, and the Cochrane ROB tool for randomized trials; total scores were calculated to classify studies as low, moderate, or high risk of bias and by using the GRADE approach to measure the quality of evidence.

The Meta Analysis Online tool[14] was used to perform meta-analysis, and the model of random-effects was applied with the inverse-variance method to account for there was anticipated clinic and methodological excesses and differences in studies. The results were generalized as standardized mean differences (SMDs) with 95% confidence intervals (CIs). I^2 statistics were used to measure heterogeneity.

The robustness of the findings was tested by performing subgroup analyses and sensitivity analyses (including leave-one-out analysis) according to intervention type, population characteristics, and study design.

Synthesis was carried out narratively in studies that could not be meta-analyzed because of heterogeneity or because the studies did not produce comparable results.

Forest plots and summary tables were used to report the results of the study, stating the study characteristics, pooled effects, and 95% confidence intervals.

12 studies were eligible with randomized and prospective interventional studies that assessed cardiac autonomic functions in T2DM patients.

RESULTS

Among the four searched electronic databases and other sources, 222 research articles were initially selected. The number was reduced to 92 records after removing the duplicates. Title and abstract screening further eliminated 30 studies. From the remaining 62 articles, 22 were removed due to unavailability of access to the full-texts. Further articles (28) were eliminated due to a lack of stratified data and studies including animals, in vitro findings, reviews, case reports, or languages other than English. Ultimately, twelve studies that passed the inclusion criteria were included in this systematic review.

The PRISMA flow diagram presented in **Figure 1** illustrates the selection process.

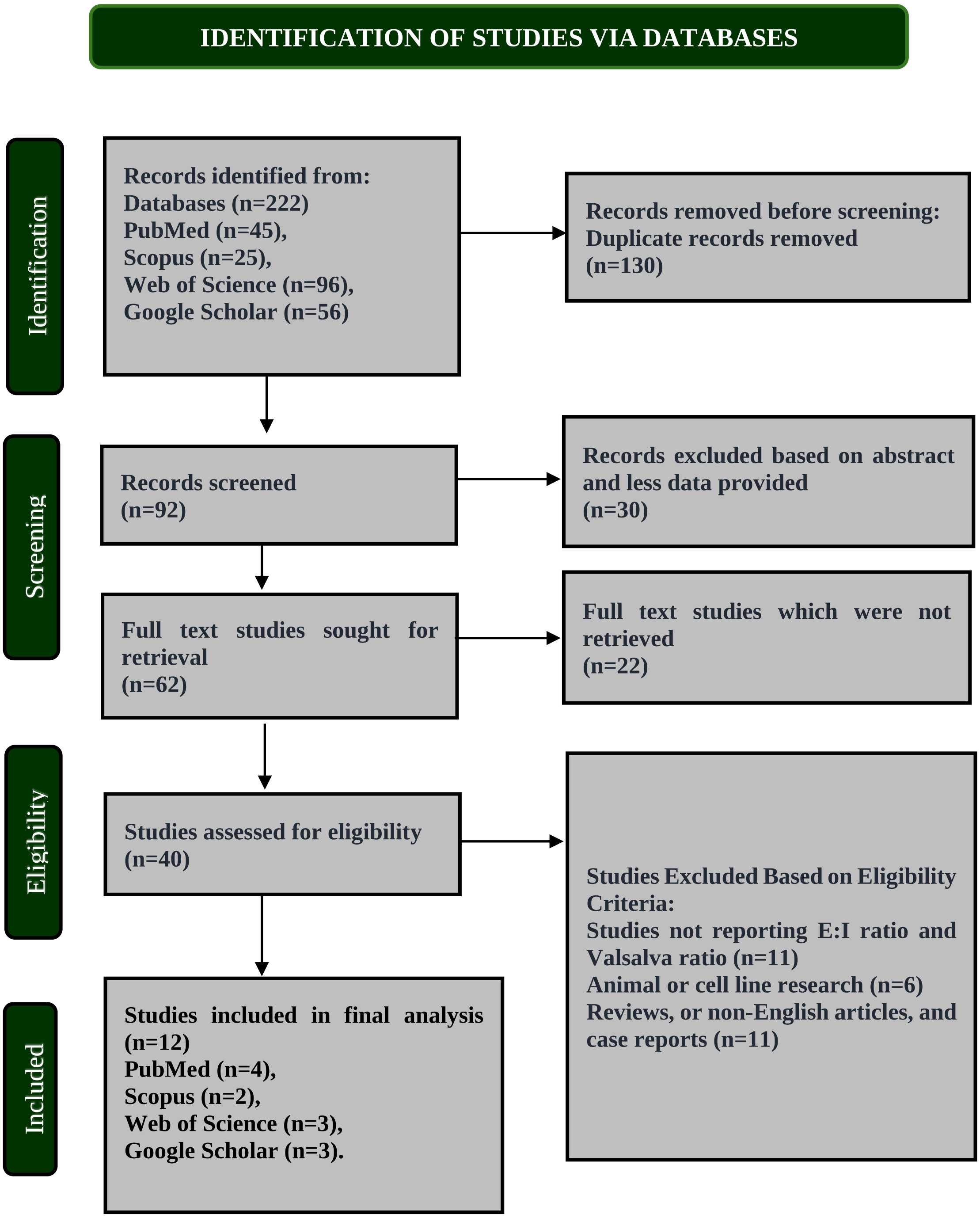


Figure 1: PRISMA Flow Diagram for Study Selection. The flowchart was designed according to the PRISMA guidelines 2020, showing study identification, screening, assessment eligibility, and final selection in the systematic review.

Table 1: Characteristics of Included Studies

Author & Year	Design	Modeling / Intervention	Population Size	Key Findings
Nganou-Gnindjio et al., 2018 [15]	Cross-sectional	Compared HRV (SDNN, SDANN) between poorly controlled (HbA1c ≥ 7%) and well-controlled T2DM	Poor control: 29; Good control: 25	The poor control group showed significantly reduced SDNN, indicating impaired autonomic modulation.
Moshenets et al., 2024 [16]	Prospective before–and–after cohort	Modified glucose-lowering therapy and assessed HRV over 6 months	T2DM: 53 (single group)	Improved glycaemic control significantly increased time- and frequency-domain HRV parameters.
Subbalakshmi et al., 2013 [17]	Case-control	Compared deep-breathing test versus diaphragmatic breathing; measured E: I ratio, r-MSSD, SDNN	Deep breathing: Type 2 diabetics 61; Controls 47. Diaphragmatic breathing: Type 2 diabetics 61; Controls 47.	T2DM patients had significantly lower E: I ratio than controls during deep breathing.
Memon et al., 2017 [18]	Cross-sectional	Bellavere's score system for assessing cardiac autonomic neuropathy (CAN)	HbA1c ≤7%: 25; HbA1c >7%: 35	Poor glycaemic control showed worse HRV, BP response, and higher CAN prevalence.
Kuriakose et al., 2025 [19]	Cross-sectional	T2DM with DPN vs without DPN	With DPN: 34; Without DPN: 34	Valsalva and E: I ratios are significantly lower in the neuropathy group, indicating worse autonomic function
Raje et al., 2025 [20]	Cross-sectional	T2DM stratified by CAN severity (Normal, Early, Definite, Severe)	Normal: 8; Early: 16; Definite: 7; Severe: 10	E: I ratio similar across CAN stages; Avg. deep breathing difference and RSA index decrease with CAN severity

Felício et al., 2025 [21]	Cross-sectional	T2DM patients with advanced kidney disease, assessed for CAN using HRV tests	Without CAN: 12; With CAN: 36	HRV parameters (VLF, LF, TP, SDNN) are significantly lower in the CAN group
Selvaraj et al., 2019 [22]	Cross-sectional	T2DM patients with different HbA1c levels, assessed by classical autonomic function tests (handgrip, deep breathing, Valsalva)	Group 1 (HbA1c <7.5%): 10; Group 2 (HbA1c 7.5–9%): 10; Group 3 (HbA1c >9%): 10	Autonomic impairment is present in all groups; no significant differences in the E/I ratio, Valsalva ratio, HR, or DBP response between HbA1c groups.
Zeng et al., 2022 [23]	Cross-sectional	HRV analysis stratified by DKD progression risk	Group A (Low risk): 187; Group B (Moderate risk): 187; Group C (High risk): 186; Group D (Very high risk): 187	HRV parameters (SDNN, LF/HF, VLF) decreased progressively with higher DKD risk
Ahmed et al., 2007 [24]	Cross-sectional	Classical autonomic function tests (E: I ratio, Valsalva ratio, HR, DBP rise, forced sinus arrhythmia, sympathetic skin response)	Diabetic: 32; Control: 34	Diabetics showed significantly lower E: I ratio, Valsalva ratio, and autonomic responses, indicating subclinical neuropathy.
Xuan et al., 2025 [25]	Randomized controlled trial	Slow deep breathing (SDB) training + mecobalamin vs control + mecobalamin	SDB: 30; Control: 30	SDB improved SDNN, RMSSD, LF, HF, and LF/HF ratio, indicating improved cardiac autonomic function
Alauddin et al., 2024 [26]	Prospective interventional study	Percutaneous coronary intervention (PCI) in T2DM patients with chronic stable angina	Pre-PCI: 30; Post-PCI: 30	Post-PCI, SDNN, RMSSD, NN50, TP, LF, HF, LF/HF ratio, E: I ratio, and Valsalva ratio significantly improved

Twelve clinical studies evaluating cardiac autonomic function in patients with type 2 diabetes mellitus were included in this systematic review, and they were done with the help of heart rate variability (HRV) and classical autonomic function tests. In general, an impaired autonomic functioning was linked to poor glycaemic control, a diabetic complication, or a developed kidney disease, but the HRV parameters were actually better upon interventions like slow deep breathing or percutaneous coronary intervention. The extent of autonomic impairment was dependent on the duration of the disease, glycaemic regulation, as well as comorbidities. Risks of bias were mostly lower to moderate, primarily because of the small samples, the focus on a single center of recruitment, or the lack of methodological description.

Table 1 is a summary of study designs, interventions, populations, and outcomes.

Table 1 includes the studies that measured cardiac autonomic functioning in type 2 diabetes mellitus patients through a heart rate variability (HRV) analysis and traditional autonomic functional assessments. The table summarizes the study design, intervention or modeling, sample size, major results on autonomic functioning, and risk of bias.

The majority of the research was in the form of cross-sectional or interventional designs that made use of standardized measurements of HRV (SDNN, RMSSD, LF, HF, LF/HF ratio) and cardiovascular reflex (E: I ratio, Valsalva ratio, handgrip, orthostasis tests) based on standard clinical protocols. In general, ineffective glycaemic control, diabetic complications, or advanced kidney disease were linked to the compromised HRV and autonomic failure, and such interventions as slow deep breathing or percutaneous coronary intervention positively influenced HRV values. Autonomic impairment was also dependent on the duration of the disease, glycaemic control, and comorbidities.

Risk of bias of the included observational and interventional studies was assessed using the Newcastle–Ottawa Scale (NOS) for cohort and cross-sectional studies, and the Cochrane ROB tool for randomized trials, with the majority of the studies being rated as moderate based on small sample sizes, single-center recruitment, or lack of description of methods. Overall, the quality of evidence used in the included studies was moderate according to GRADE. The risk of bias is given in **Table 2** and **3**.

Table 2: Risk of Bias of Included Studies

Study	Selection (max 4)	Comparability (max 2)	Outcome (max 3)	Total (max 9)	Risk of Bias

Nganou-Gnindjio et al., 2018	★★★	★★	★★	7	Moderate
Moshenets et al., 2024	★★★	★★	★★	7	Moderate
Subbalakshmi et al., 2013	★★★	★★	★★	7	Moderate
Memon et al., 2017	★★★	★★	★★	7	Moderate
Kuriakose et al., 2025	★★★	★★	★★	7	Moderate
Raje et al., 2025	★★★	★★	★★	7	Moderate
Felício et al., 2025	★★★★	★★	★★★	9	Low
Selvaraj et al., 2019	★★★	★★	★★	7	Moderate
Zeng et al., 2022	★★★	★★	★★	7	Moderate
Ahmed et al., 2007	★★★	★★	★★	7	Moderate
Alauddin et al., 2024	★★★	★★	★★	7	Moderate

Total Score (max 9): Higher scores indicate lower risk of bias. 7–9: Low risk, 4–6: Moderate risk, <4: High risk.

Table 3: Risk of Bias of RCTs

Study	**Random Sequence Generation**	**Allocation Concealment**	**Blinding (Participants & Personnel)**	**Blinding (Outcome Assessment)**	**Incomplete Data**	**Selective Reporting**	**Other Bias**	**Overall RoB**
Xuan et al., 2025	+	+	+	+	+	+	±	Moderate

+ Low risk, ± Some concerns / Moderate, − High risk

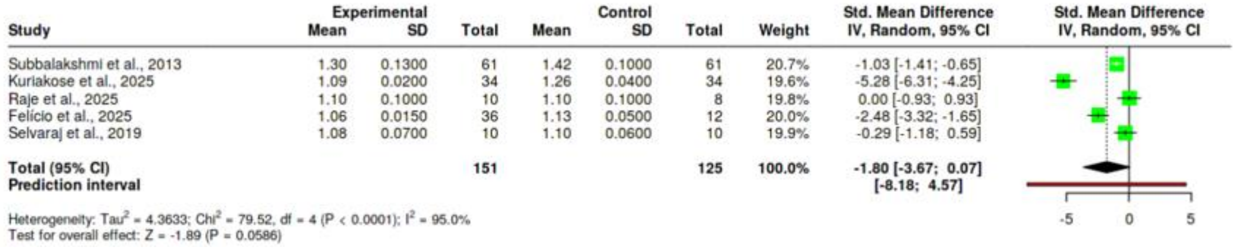
Meta-Analysis

The meta-analysis evaluated the cardiac autonomic functioning in type 2 diabetes mellitus (T2DM) patients under two main outcomes: these are the E: I ratio (deep-breathing) and the Valsalva ratio. There were various studies that added to each of the outcomes. All associations were calculated in the Meta Analysis Online tool based on a random-effects analysis model through the use of the inverse-variance methodology, which was preconceived to incorporate the anticipated clinical and methodology differences across study protocols, patient populations, and methods of measurement.

In the case of E:I ratio, the pooling of data consisted of 151 experimental and 125 control subjects in 5 studies. The resultant effect was a standardized mean difference (SMD) = -1.80 (95% CI: -3.67 0.07), which was not statistically significant (overall effect $p > 0.05$).

Between-study heterogeneity was, however, high ($I^2 = 95\%$, $p < 0.01$), implying that most of the differences observed between the studies may not be because of sampling error but because the studies might have actually been different.

The forest plot of the standardized mean difference (SMD) of E: I ratio of experimental and control groups is presented in **Figure 2**.



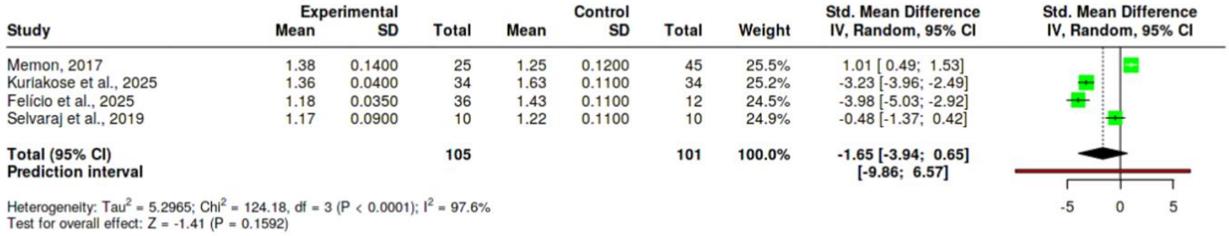
Study	Experimental Mean	Experimental SD	Total	Control Mean	Control SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Subbalakshmi et al., 2013	1.30	0.1300	61	1.42	0.1000	61	20.7%	-1.03 [-1.41; -0.65]
Kuriakose et al., 2025	1.09	0.0200	34	1.26	0.0400	34	19.6%	-5.28 [-6.31; -4.25]
Raje et al., 2025	1.10	0.1000	10	1.10	0.1000	8	19.8%	0.00 [-0.93; 0.93]
Felício et al., 2025	1.06	0.0150	36	1.13	0.0500	12	20.0%	-2.48 [-3.32; -1.65]
Selvaraj et al., 2019	1.08	0.0700	10	1.10	0.0600	10	19.9%	-0.29 [-1.18; 0.59]
Total (95% CI)			**151**			**125**	**100.0%**	**-1.80 [-3.67; 0.07]**
Prediction interval								**[-8.18; 4.57]**

Heterogeneity: $Tau^2 = 4.3633$; $Chi^2 = 79.52$, $df = 4$ ($P < 0.0001$); $I^2 = 95.0\%$
Test for overall effect: $Z = -1.89$ ($P = 0.0586$)

Figure 2: Forest plot of the standardized mean differences (SMD) and 95% confidence intervals of E: I ratio in T2DM patients. Individual study estimates are represented as squares, and the size symbolizes the weight of a study. 95% CIs are denoted by horizontal lines. The SMD of pools is presented as a diamond at the bottom. Those values to the left of the line are in favor of the experimental group; those to the right of the line are in favor of controls.

In the case of the Valsalva ratio, the combined analysis comprised 105 experimental and 101 control participants in 4 studies. The effect size was a standardized mean difference (SMD) = -1.65 (95% CI: -3.94 to 0.65), which was not statistically significant (overall effect $p > 0.05$). The degree of heterogeneity ($I^2 = 98\%$, $p < 0.01$) once again was very high in nature because there was an inconsistent magnitude of the effects and the reversal of the direction of the effect in some of the studies.

Figure 3 provides the standardized mean difference (SMD) of the Valsalva ratio of the experimental group and control group in the form of a forest plot.



Study	Experimental Mean	Experimental SD	Total	Control Mean	Control SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Memon, 2017	1.38	0.1400	25	1.25	0.1200	45	25.5%	1.01 [0.49; 1.53]
Kuriakose et al., 2025	1.36	0.0400	34	1.63	0.1100	34	25.2%	-3.23 [-3.96; -2.49]
Felício et al., 2025	1.18	0.0350	36	1.43	0.1100	12	24.5%	-3.98 [-5.03; -2.92]
Selvaraj et al., 2019	1.17	0.0900	10	1.22	0.1100	10	24.9%	-0.48 [-1.37; 0.42]
Total (95% CI)			**105**			**101**	**100.0%**	**-1.65 [-3.94; 0.65]**
Prediction interval								**[-9.86; 6.57]**

Heterogeneity: $Tau^2 = 5.2965$; $Chi^2 = 124.18$, df = 3 ($P < 0.0001$); $I^2 = 97.6\%$
Test for overall effect: $Z = -1.41$ ($P = 0.1592$)

Figure 3: Forest plot of the standardized mean differences (SMD) and 95% CI of the Valsalva ratio among patients with T2DM. The squares represent the individual study estimates, and size is used to represent study weight; 95% CIs are represented as horizontal lines. A diamond is used as a representation of the pooled SMD.

Taken together, these research studies suggest that in the majority of the studies, there is no significant difference in E: I ratio or Valsalva ratio between experimental and control cohorts of T2DM patients. This fact points to the fact that the variability in the study protocol, patient characteristics, and measurement methods has a significant impact on the pooled effect estimates.

This degree of heterogeneity is how high the level of interpretation of pooled effect sizes by clinicians and researchers should be interpreted with care.

Subgroup Analysis

Subgroup analysis was taken into consideration where possible, depending on the severity of the CAN and on the glycaemic control. Even though certain subgroups tended to decrease autonomic functioning in experimental cohorts, none of them exhibited a significant pooled effect. The heterogeneity was high within the subgroups, which means that study population variability and methods variability have a strong impact on results.

Sensitivity Analysis

Sensitivity analyses based on the leave-one-out showed that the direction of the pooled effect on both outcomes was not reversed as individual studies were left out. The drop of heterogeneity by exclusion of large-weight studies was small but did not influence the general findings, which supports the idea that the non-significant pooled effects are strong.

DISCUSSION

Cardiac autonomic neuropathy (CAN) is among the most important cardiovascular complications of type 2 diabetes mellitus (T2DM), which occurs as a result of prolonged hyperglycemia, oxidative stress, and microvascular damage, which, in combination, dysregulate autonomic control of the heart [27]. Pathophysiology of CAN is a complicated combination of neuronal damage, endothelial dysfunction, and abnormal autonomic communication resulting in reduced parasympathetic tone and sympathetic hyperactivity [28]. This autonomic dysregulation predisposes patients with T2DM to arrhythmias, silent myocardial ischemia, and sudden cardiac death, and, therefore, there is an urgent necessity to implement interventions to maintain or recover autonomic functioning in patients with T2DM [29].

The cardiac autonomic neuropathy is a problem that should be recognized early since in most cases, the autonomic impairment causes no symptoms and hence may be hidden until very advanced stages [30]. Noninvasive measurements like heart rate variability, time domain (SDNN, RMSSD) and frequency domain measures (LF, HF, LF/HF ratio), cardiovascular reflex tests like the E:I ratio and Valsalva ratio are all good indicators of parasympathetic and sympathetic activity. Periodic assessment enables clinicians to detect patients with high risks and implement maneuvers that are intended to maintain or regain autonomic equilibrium [31].

Modifiable and non-modifiable factors that control the development and course of CAN are a number. Oxidative stress and microvascular damage result in chronic hyperglycemia and cause accelerated neuronal damage and disrupted autonomic signaling [32]. Autonomic dysfunction is also further caused by insulin resistance, hypertension, dyslipidemia, obesity, and lifestyle factors including physical inactivity and smoking [33]. Also, comorbid conditions like diabetic nephropathy, retinopathy, and peripheral neuropathy are linked to a more severe autonomic impairment, and multifaceted metabolic and cardiovascular management of patients with type 2 diabetes should be noted [34].

Therapy of CAN is aimed at glycaemic control, pharmacological therapy, lifestyle change, and operative therapy. The measures of heart rate variability and parasympathetic sysytem can be optimized by the use of medications, structured exercise programs, as well as stress reduction techniques [35]. Aerobic exercises and slow deep breathing have been demonstrated to increase autonomic tone and cardiovascular reflexive responses and are known as non-pharmacological interventions [36]. Percutaneous coronary intervention as one of the revascularization techniques can be used to facilitate the process of autonomic restoration in patients with coexisting coronary artery disease. Integrating these interventions, which are patient-specific, offers the best modality towards the prevention of the escalation of CAN and cardiovascular morbidity and mortality in type 2 diabetes [37].

Interventional interventions against CAN have been investigated more often, with the pharmacological options of glucose-lowering and cardiovascular modulators, to the non-pharmacological interventions of slow deep breathing (SDB), regular exercise schemes, and mind-body therapies [38]. These interventions intend to enhance heart rate variability (HRV), E: I ratio, and Valsalva ratio as proxies of parasympathetic and sympathetic balance. It is also postulated that the glycaemic optimization with lifestyle or procedural interventions may prove to be more beneficial in the autonomic outcome than single-modality methods [39].

These interventions depend on various factors such as the duration of diabetes, the level of glycaemic control at the onset, the severity of neuropathy, and comorbidities such as diabetic kidney disease, hypertension, and cardiovascular disease, among others [40]. A history of hyperglycemia and advanced neuropathy are some of the factors that reduce the possibility of reversibility and put the importance of diagnosis and timely intervention on the issue into perspective [41]. Also, the unique variability of response can be based on genetic factors, lifestyle habits, adherence to medications, and pre-existing cardiovascular status, which promotes the idea of patient-specific approaches [42].

Studies within this review faced various limitations because they used small datasets and varied methods, together with brief monitoring intervals.

Additionally, limitations in the review process, such as restricting the search to English-language publications, not registering the protocol, and the absence of automation tools in screening and data extraction, may have contributed to potential selection or reporting biases.

On the whole, the evidence gathered so far suggests the potential of both pharmacological and non-pharmacological approaches to cardiac autonomic function preservation or improvement in the case of T2DM. The most promising seem to be multimodal approaches, especially those involving the combination of glycaemic optimization and lifestyle or procedural interventions. To explain the underlying pathways and maximize the therapeutic outcomes, future studies should concentrate on large, multicenter randomized trials that utilize standardized protocols, stratified patient populations, and also mechanistic biomarkers. Moreover, introducing continuous monitoring and sophisticated HRV analytics can offer more delicate and tangible intervention efficacy measures, which will eventually inform clinical practice of CAN.

CONCLUSION

Finally, T2DM patients using interventions show inconsistent and unstable changes in E: I and Valsalva ratios, which show continuing cardiac autonomic dysfunction. The great heterogeneity of the studies does not allow conclusive judgments, but the data indicate that non-pharmacological, pharmacological, and multimodal approaches may have some benefits, especially in association with optimized glycaemic control. Well-designed, standardized trials that are larger, use homogeneous measures of outcome, and have extended follow-up are needed to determine effective prevention and mitigation strategies to prevent and reduce CAN. Such evidence-based interventions can eventually enhance the outcome of cardiovascular diseases, minimize morbidity and mortality, and improve long-term prognosis in patients with T2DM.

LIST OF ABBREVIATIONS

HRV: Heart Rate Variability

E:I ratio: Expiratory-To-Inspiratory Ratio

SDNN: Standard Deviation of NN Intervals

RMSSD: Root Mean Square of Successive Differences

LF: Low Frequency

HF: High Frequency

TP: Total Power

NN50: Number of Pairs of Successive NN Intervals Differing By >50 ms

CAN: Cardiac Autonomic Neuropathy

PCI: Percutaneous Coronary Intervention

SDB: Slow Deep Breathing

ACKNOWLEDGMENTS

None

FUNDING

None.

CONFLICT OF INTEREST

None.

AUTHORS' CONTRIBUTION

USAS: Conceptualization, protocol design, literature search strategy formulation, drafting the manuscript, and final approval. **MZB:** Study screening (title/abstract and full-text), data extraction, statistical analysis (meta-analysis execution), drafting the methodology, and final approval. **MDK:** Study screening (title/abstract and full-text), data extraction, risk of bias/quality assessment, revising the manuscript critically, and final approval. **KZ:** Risk of bias/quality assessment, acting as the third reviewer for screening disagreements, data interpretation, critical revision of the manuscript for intellectual content, and final approval.

REFERENCES

1. Soe KK, Selvarajah D. Cardiac Autonomic Neuropathy and Its Impact on Progression of Diabetic Kidney Disease in Type 1 and Type 2 Diabetes. *Kidney Med* 2025;7:101149. doi:10.1016/j.xkme.2025.101149

2. Gogan A, Potre O, Avram V-F, Andor M, Caruntu F, Timar B, et al. Cardiac Autonomic Neuropathy in Diabetes Mellitus: Pathogenesis, Epidemiology, Diagnosis and Clinical Implications: A Narrative Review. *J Clin Med* 2025;14. doi:10.3390/jcm14030671

3. Damoun N, Amekran Y, Taiek N, Hangouche AJE. Heart rate variability measurement and influencing factors: Towards the standardization of methodology. *Glob Cardiol Sci Pract* 2024:e202435. doi:10.21542/gcsp.2024.35

4. Duque A, Mediano MFF, De Lorenzo A, Rodrigues LF Jr. Cardiovascular autonomic neuropathy in diabetes: Pathophysiology, clinical assessment and implications. *World J Diabetes* 2021;12:855–67. doi:10.4239/wjd.v12.i6.855

5. Ashinze P, Gaur A, Banerjee S, Olaniyan OM, Akande E, Idris-Agbabiaka A, et al. The role of heart rate variability in cardiac surgery: applications and innovations. *Cardiothorac Surg* 2025;33:34. doi:10.1186/s43057-025-00179-9

6. Míková M, Pospíšil D, Řehoř J, Malik M. Heart Rate Variability Analysis in Congestive Heart Failure: The Need for Standardized Assessment Protocols. *Rev Cardiovasc Med* 2025;26:36321. doi:10.31083/RCM36321

7. John APP, Udupa K, Avangapur S, Sujan MU, Inbaraj G, Vasuki PP, et al. Cardiac autonomic dysfunctions in type 2 diabetes mellitus: an investigative study with heart rate variability measures. *Am J Cardiovasc Dis* 2022;12:224–32.

8. Al-Ozairi E, Jallo MK, Hafidh K, Alhajeri DM, Ashour T, Mahmoud EFN, et al. Prevalence of Cardiovascular and Renal Co-morbidities in Patients with Type 2 Diabetes in the Gulf, a Cross-sectional Observational Study. *Diabetes Ther* 2021;12:1193–207. doi:10.1007/s13300-021-01038-6

9. Gieroba B, Kryska A, Sroka-Bartnicka A. Type 2 diabetes mellitus – conventional therapies and future perspectives in innovative treatment. *Biochem Biophys Rep* 2025;42:102037. doi:10.1016/j.bbrep.2025.102037

10. Bhat S, Yatsynovich Y, Sharma UC. Coronary revascularization in patients with stable coronary disease and diabetes mellitus. *Diab Vasc Dis Res* 2021;18:14791641211002469. doi:10.1177/14791641211002469

11. Zhang W, Bi S, Luo L. The impact of long-term exercise intervention on heart rate variability indices: a systematic meta-analysis. *Front Cardiovasc Med* 2025;12:1364905. doi:10.3389/fcvm.2025.1364905

12. Zaki S, Alam MF, Sharma S, El-Ashker S, Ahsan M, Nuhmani S, et al. Impact of Concurrent Exercise Training on Cardiac Autonomic Modulation, Metabolic Profile, Body Composition, Cardiorespiratory Fitness, and Quality of Life in Type 2 Diabetes with Cardiac Autonomic Neuropathy: A Randomized Controlled Trial. *J Clin Med* 2024;13. doi:10.3390/jcm13133910

13. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi:10.1136/bmj.n71

14. metaanalysisonline.com. [Internet]. 2025 [cited 2025 Oct 19]. Available from: https://metaanalysisonline.com/

15. Nganou-Gnindjio CN, Mba CM, Azabji-Kenfack M, Dehayem MY, Mfeukeu-Kuate L, Mbanya J-C, et al. Poor glycemic control impacts heart rate variability in patients with type 2 diabetes mellitus: a cross sectional study. *BMC Res Notes* 2018;11:599. doi:10.1186/s13104-018-3692-z

16. Moshenets K, Pertseva N. The impact of glycemic control on heart rate variability in patients with type 2 Diabetes Mellitus and the potential for prediction. *Romanian J Diabetes Nutr Metab Dis* 2024;31:441–7.

17. Subbalakshmi NK, Adhikari P, Shanmugavel Jeganathan P. Comparative study on cardiac autonomic modulation during deep breathing test and diaphragmatic breathing in type 2 diabetes and healthy subjects. *J Diabetes Investig* 2014;5:456–63. doi:10.1111/jdi.12163

18. Memon A. Cardiac autonomic neuropathy in type 2 diabetes mellitus using Bellavere's score system. *Int J Health Sci* 2017;11:26–9.

19. Kuriakose S, Singhal A, Bansal N, Shukla R, Paul SM, Singhal A. A Study on Autonomic Dysfunction in Type 2 Diabetes Mellitus with Peripheral Neuropathy. *J Mar Med Soc* 2025;27:24. doi:10.4103/jmms.jmms_6_24

20. Raje S, Maiya GA, R P, Prabhu MA, Nayak K, Shivashankara KN, et al. Prediction of cardiac autonomic dysfunction using heart rate response to deep breathing test among type 2 diabetes mellitus. *BMC Endocr Disord* 2025;25:117. doi:10.1186/s12902-025-01939-8

21. Felício JS, Araújo MAM, de Lemos GN, Fernandes IJ, Ruivo LO, Chambouleyron EG, et al. Heart rate variability tests for diagnosing cardiovascular autonomic neuropathy in patients with type 2 diabetes mellitus in advanced stages of kidney disease. *Cardiovasc Diabetol* 2025;24:144. doi:10.1186/s12933-025-02666-z

22. Jayabal M, Kumar Selvaraj V, Subramaniam M, Shivalingiaya J, Ramanathan R. Classical autonomic function tests in type 2 diabetes mellitus patients with different HbA1c levels: A comparative study. *Indian J Clin Anat Physiol* 2019;6:23–6. doi:10.18231/2394-2126.2019.0006

23. Zeng H, Liu J, Chen Z, Yu P, Liu J. Cardiac Autonomic Dysfunction Is Associated With Risk of Diabetic Kidney Disease Progression in Type 2 Diabetes Mellitus. *Front Endocrinol* 2022;13:900465. doi:10.3389/fendo.2022.900465

24. Ahmed TS, Al-Maatouq MA, Al-Tuwaijri AS. Subclinical autonomic neuropathy in Saudi type 2 diabetic patients. *12*

25. Xuan M, Shen Y, Tang W, Fang P, Liu G, Li G, et al. Effect of slow deep breathing on cardiovascular autonomic neuropathy in type 2 diabetes mellitus patients. *Diabetol Metab Syndr* 2025;17:330. doi:10.1186/s13098-025-01862-x

26. Alauddin W, Radke PM, Pardhi P, Mishra M, Arora S. Effects of Revascularization on Cardiac Autonomic Neuropathy in Type 2 Diabetes Mellitus Patients With Chronic Stable Angina. *Cureus* 2024;16:e72278. doi:10.7759/cureus.72278

27. Yang Y, Zhao B, Wang Y, Lan H, Liu X, Hu Y, et al. Diabetic neuropathy: cutting-edge research and future directions. *Signal Transduct Target Ther* 2025;10:132. doi:10.1038/s41392-025-02175-1

28. Mehra R, Tjurmina OA, Ajijola OA, Arora R, Bolser DC, Chapleau MW, et al. Research Opportunities in Autonomic Neural Mechanisms of Cardiopulmonary Regulation: A Report From the National Heart, Lung, and Blood Institute and the National Institutes of Health Office of the Director Workshop. *JACC Basic Transl Sci* 2022;7:265–93. doi:10.1016/j.jacbts.2021.11.003

29. Kaze AD, Fonarow GC, Echouffo-Tcheugui JB. Cardiac Autonomic Dysfunction and Risk of Silent Myocardial Infarction Among Adults With Type 2 Diabetes. *J Am Heart Assoc* 2023;12:e029814. doi:10.1161/JAHA.123.029814

30. Zilliox LA, Russell JW. Is there cardiac autonomic neuropathy in prediabetes? *Auton Neurosci* 2020;229:102722. doi:10.1016/j.autneu.2020.102722

31. Oliveira DPSC, Souza QS, Facchin AC, Mariano BC, Silva LP, Peçanha T. Diagnostic value of heart rate-based methods for assessing cardiac autonomic neuropathy in prediabetes and diabetes. *Physiol Rep* 2025;13:e70610. doi:10.14814/phy2.70610

32. Zakir M, Ahuja N, Surksha MA, Sachdev R, Kalariya Y, Nasir M, et al. Cardiovascular Complications of Diabetes: From Microvascular to Macrovascular Pathways. *Cureus* 15:e45835. doi:10.7759/cureus.45835

33. Espinoza-Salinas A, Molina-Sotomayor E, Cano-Montoya J, Gonzalez-Jurado JA, Espinoza-Salinas A, Molina-Sotomayor E, et al. Is Active Lifestyle Related to Autonomic Nervous System Function and Lipid Profile in People with Overweight? A Study Pilot. *Sustainability* 2021;13. doi:10.3390/su13052439

34. Kulkarni A, Thool AR, Daigavane S. Understanding the Clinical Relationship Between Diabetic Retinopathy, Nephropathy, and Neuropathy: A Comprehensive Review. *Cureus* 2024;16:e56674. doi:10.7759/cureus.56674

35. Thal SC, Shityakov S, Salvador E, Förster CY, Thal SC, Shityakov S, et al. Heart Rate Variability, Microvascular Dysfunction, and Inflammation: Exploring the Potential of taVNS in Managing Heart Failure in Type 2 Diabetes Mellitus. *Biomolecules* 2025;15. doi:10.3390/biom15040499

36. Liu X, Shan Z, Shen T, Lo M, Luo L, Sun Q, et al. Individualized paced deep breathing training with autonomic nervous function as rehab targets in patients with chronic heart failure: a randomized clinical trial. *Int J Cardiol Heart Vasc* 2025;61:101800. doi:10.1016/j.ijcha.2025.101800

37. Abubakar M, Javed I, Rasool HF, Raza S, Basavaraju D, Abdullah RM, et al. Advancements in Percutaneous Coronary Intervention Techniques: A Comprehensive Literature Review of Mixed Studies and Practice Guidelines. *Cureus* 15:e41311. doi:10.7759/cureus.41311

38. Obaya HE, Abdeen HA, Salem AA, Shehata MA, Aldhahi MI, Muka T, et al. Effect of aerobic exercise, slow deep breathing and mindfulness meditation on cortisol and glucose levels in women with type 2 diabetes mellitus: a randomized controlled trial. *Front Physiol* 2023;14:1186546. doi:10.3389/fphys.2023.1186546

39. Bekker I, Kooistra A, van Dijk PR, Lefrandt JD, Veeger NJGM, van Beek AP. The Influence of Exercise and Physical Activity on Autonomic Nervous System Function Measured by Heart Rate Variability in Individuals with Type 1 Diabetes Mellitus—A Systematic Review. *Int J Mol Sci* 2025;26:7096. doi:10.3390/ijms26157096

40. Nabrdalik K, Kwiendacz H, Moos J, Moos Ł, Kulpa J, Brzoza Z, et al. Diabetic Peripheral Neuropathy is Associated With Diabetic Kidney Disease and Cardiovascular Disease: The Silesia Diabetes-Heart Project. *Curr Probl Cardiol* 2023;48:101726. doi:10.1016/j.cpcardiol.2023.101726

41. Smith S, Normahani P, Lane T, Hohenschurz-Schmidt D, Oliver N, Davies AH, et al. Prevention and Management Strategies for Diabetic Neuropathy. *Life* 2022;12. doi:10.3390/life12081185

42. Almutairi M, Almutairi AA, Alodhialah AM, Almutairi M, Almutairi AA, Alodhialah AM. The Influence of Lifestyle Modifications on Cardiovascular Outcomes in Older Adults: Findings from a Cross-Sectional Study. *Life* 2025;15. doi:10.3390/life15010087