RESEARCH PAPER

Elucidation of Non Pharmacological Management of Cardiac Autonomic Neuropathy Affecting HRV and Cardiovascular Outcomes: A Review

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ABSTRACT

Background
Cardiac autonomic neuropathy (CAN) is a common complication of diabetes associated with reduced heart rate variability (HRV) and increased cardiovascular mortality. While pharmacological treatment mainly addresses symptoms, non pharmacological interventions such as structured exercise may improve autonomic function, though evidence from randomized controlled trials remains scattered.

Objective
This systematic review aimed to synthesize available RCT evidence on the effects of non pharmacological interventions on HRV in patients with CAN.

Methods
Following PRISMA guidelines, databases including PubMed, Embase, Cochrane CENTRAL, Scopus, Web of Science, and Google Scholar were searched for studies published between 2015 and 2025. Eleven RCTs met the inclusion criteria, involving adults with confirmed CAN who underwent aerobic, resistance, or combined exercise interventions with HRV as the primary outcome. Due to heterogeneity in study designs and outcome measures, a narrative synthesis was performed.

Result
The review found that combined aerobic resistance exercise produced the greatest improvements in HRV indices, with additional benefits observed in autonomic reflex measures, cardiorespiratory fitness, and resting heart rate. Home based exercise programs showed high adherence and sustained improvements, and no serious adverse events were reported.In conclusion, non pharmacological exercise interventions are safe and effective in improving autonomic function in patients with early to moderate CAN. Home based combined exercise programs appear particularly promising, although further large scale trials with standardized protocols and long term outcomes are required.

Keywords: *cardiac autonomic neuropathy, heart rate variability, exercise training, non-pharmacological intervention, autonomic dysfunction*
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1. INTRODUCTION

Cardiac autonomic neuropathy (CAN) is one of the most serious, underdiagnosed complications of diabetes mellitus, characterized by damage to the autonomic fibers that innervate the heart and blood vessels, resulting in impaired regulation of heart rate, vascular tone, and blood pressure (Pop-Busui et al., 2019; Spallone, 2018). Clinically, CAN manifests along a continuum from early subclinical abnormalities detectable only with specialized cardiovascular autonomic reflex tests (CARTs) and heart rate variability (HRV) analysis, to advanced stages marked by resting tachycardia, exercise intolerance, orthostatic hypotension, silent myocardial ischemia, and increased risk of sudden cardiac death (Vinik et al., 2017, Aditi & Rai, 2026a).

Epidemiological evidence suggests that CAN affects approximately 20–65% of individuals with diabetes, with prevalence rising with longer disease duration, poor glycemic control, and coexisting microvascular complications such as retinopathy and nephropathy (Evaluating Cardiovascular Autonomic Neuropathy in Diabetes, 2023). Importantly, the presence of CAN has been associated with a near two-fold increase in cardiovascular mortality, independent of traditional risk factors, highlighting its prognostic importance and the need for effective interventions (Spallone, 2018; Vinik et al., 2017).

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The assessment of CAN relies on standardized diagnostic procedures that capture the integrity of autonomic control over the cardiovascular system. The Ewing battery, considered the gold standard, includes tests such as heart rate response to deep breathing (expressed as the expiration–inspiration ratio), the Valsalva maneuver, heart rate response to standing (30:15 ratio), and blood pressure response to postural change (Ewing et al., 1985; Vinik et al., 2017).

In addition to these reflex tests, HRV analysis has emerged as a sensitive, non-invasive method to quantify beat-to-beat fluctuations in heart rate, reflecting the interplay between sympathetic and parasympathetic (vagal) inputs at the sinus node (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). Time-domain indices, such as the standard deviation of all normal-to-normal intervals (SDNN), the root mean square of successive differences (RMSSD), and the percentage of adjacent NN intervals differing by more than 50 ms (pNN50), capture overall variability and short-term parasympathetic modulation.

Frequency-domain indices, including low-frequency power (LF), high-frequency power (HF), and the LF/HF ratio, provide insight into sympathovagal balance, with HF primarily reflecting vagal activity and the LF/HF ratio commonly interpreted as an index of sympathovagal shift (Task Force, 1996; Picard et al., 2021). Reductions in SDNN and RMSSD, suppression of HF power, and elevation of LF/HF ratio are consistently observed in patients with CAN and have been linked to increased risk of ventricular arrhythmias, myocardial infarction, and mortality in both diabetic and non-diabetic cohorts (Heart Rate Variability and Cardiac Autonomic Dysfunction in Diabetes, 2019; Aditi & Rai, 2026b; Picard et al., 2021).

Pathophysiologically, CAN develops through a complex interplay of chronic hyperglycemia, oxidative stress, advanced glycation end-products, microvascular ischemia, and low-grade inflammation leading to structural and functional damage of autonomic nerve fibers (Pop-Busui et al., 2019; Gupta et al., 2026a; Vinik et al., 2017). Hyperglycemia-induced metabolic derangements, including activation of the polyol pathway and protein kinase C, promote neural ischemia and demyelination, while impaired nitric oxide bioavailability and endothelial dysfunction further compromise baroreflex function and vascular reactivity (Spallone, 2018; Bhati et al., 2022). Over time, this contributes to a characteristic pattern of autonomic imbalance: early withdrawal of vagal tone, followed by sympathetic overactivity and eventual sympathetic failure in advanced stages. Clinically, this translates to resting tachycardia, exercise intolerance, reduced HRV, abnormal blood pressure responses, and impaired ability to respond to hemodynamic stressors such as exercise, hypoglycemia, or postural change (Vinik et al., 2017; Heart Rate Variability and Cardiac Autonomic Dysfunction in Diabetes, 2019; Ayushi et al., 2026; Pinki et al., 2025). Because these abnormalities may remain asymptomatic for prolonged periods, early detection through HRV assessment and CARTs is essential to prevent progression and guide individualized management strategies.

Conventional management of CAN has predominantly focused on pharmacological optimization of cardiovascular and metabolic risk factors. Tight glycemic control, blood pressure management with renin–angiotensin system blockers, lipid-lowering therapy, and antiplatelet agents form the cornerstone of cardiovascular prevention in diabetes (Pop-Busui et al., 2019; Baweja et al., 2026). Symptomatic treatments such as fludrocortisone, midodrine, or droxidopa may be prescribed for orthostatic hypotension, while beta-blockers and other anti-arrhythmic agents may be used in selected cases to control heart rate and prevent arrhythmias (Spallone, 2018; Vinik et al., 2017). However, these pharmacological strategies rarely reverse autonomic dysfunction and are often limited by side effects, contraindications, and polypharmacy in patients with multiple comorbidities. Consequently, there is growing interest in non-pharmacological interventions that can directly modulate autonomic function, improve HRV, and potentially alter the natural history of CAN.

Among non-pharmacological strategies, structured exercise training has emerged as a particularly promising modality. Aerobic training, resistance training, and combined aerobic–resistance programs have been shown to improve endothelial function, enhance insulin sensitivity, reduce systemic inflammation, and increase cardiorespiratory fitness mechanisms that may collectively lead to restoration of vagal tone and improved baroreflex sensitivity (Farias et al., 2021; Gupta et al., 2026b; Kumar et al., 2025; Picard et al., 2021). Experimental and clinical data suggest that regular exercise can increase HF power, normalize LF/HF ratios, and improve time-domain HRV measures in various cardiometabolic populations, including those with type 2 diabetes (Picard et al., 2021; Lopes et al., 2023). In patients with established CAN or diabetic kidney disease, home-based and supervised exercise programs have demonstrated improvements in SDNN, RMSSD, HF power, baroreflex sensitivity, and cardiovascular autonomic reflex test performance, indicating a favorable shift toward parasympathetic predominance (Michou et al., 2023a; Hussain et al., 2025; Michou et al., 2023b; Shafeek et al., 2023). These findings suggest that exercise may serve not only as a supportive component of diabetes management but as a disease-modifying intervention for CAN itself.

More recently, several randomized controlled trials have specifically examined the effects of different exercise modalities and delivery formats on HRV and cardiovascular autonomic outcomes in populations with confirmed autonomic dysfunction or high CAN risk. For example, Michou et al. (2023a, 2023b) reported that home-based, moderate-intensity aerobic–resistance training improved time- and frequency-domain HRV indices and autonomic reflex responses in patients with diabetic kidney disease and in kidney transplant recipients

with diabetes. Shafeek et al. (2023) observed that supervised aerobic training improved baroreflex sensitivity and HRV in patients with type 2 diabetes and diabetic kidney disease. Zaki et al. (2024b) demonstrated that the sequence of concurrent exercise (aerobic first versus resistance first) differentially influenced HRV responses and LF/HF ratio reduction in patients with type 2 diabetes and cardiovascular autonomic neuropathy, suggesting that exercise prescription details may meaningfully affect autonomic outcomes. Other RCTs have explored high-intensity interval training, mixed home-based programs, or combined modality interventions, with varying degrees of improvement in HRV, VO_2peak, resting heart rate, and CAN severity scores (Farias et al., 2021; Su et al., 2022; Vágvölgyi et al., 2023; Zaki et al., 2024a).

Despite this growing body of evidence, several important gaps remain. First, existing trials differ substantially in CAN diagnostic criteria (e.g., Ewing battery thresholds versus HRV cut-offs), HRV measurement protocols (short-term versus 24-hour recordings, device heterogeneity), and exercise prescriptions (intensity, volume, supervision level, and duration), making it difficult to generalize findings to routine clinical practice (Lopes et al., 2023; Picard et al., 2021). Second, many trials are limited by small sample sizes, short intervention periods (often 8–12 weeks), and limited follow-up, restricting inferences about long-term cardiovascular outcomes, sustainability of HRV improvements, and effects on hard endpoints such as arrhythmias, myocardial infarction, or mortality. Third, there has been limited synthesis focusing specifically on individuals with confirmed CAN as opposed to broader populations with diabetes despite the distinct risk profile and pathophysiological characteristics of this subgroup (Lopes et al., 2023). Finally, the relative efficacy of different exercise modalities (aerobic versus resistance versus combined) and delivery models (home-based versus center-based) on specific HRV domains (time versus frequency) remains incompletely understood.

Accordingly, there is a clear need for a focused synthesis of randomized controlled trial evidence examining non-pharmacological interventions, particularly structured exercise training, in patients with established CAN. This systematic review aims to address these gaps by collating and critically appraising RCTs that evaluate the effects of non-pharmacological interventions on HRV and cardiovascular autonomic outcomes in adults with confirmed CAN. The primary objective is to determine the impact of these interventions on HRV time-domain indices (SDNN, RMSSD, pNN50) and frequency-domain indices (LF, HF, LF/HF ratio). Secondary objective include assessing the effects on cardiovascular autonomic reflex tests (Valsalva ratio, E/I ratio, 30:15 ratio, postural blood pressure change), baroreflex sensitivity, resting heart rate, exercise capacity (VO_2peak, six-minute walk distance), blood pressure variability, and composite CAN severity scores. In addition, this review explores the influence of exercise type (aerobic, resistance, combined), intervention duration, and delivery setting (home-based versus supervised) on observed outcomes, and evaluates safety, adherence, and methodological quality across studies.

By integrating data from contemporary randomized trials, this review seeks to provide clinicians, physiotherapists, and researchers with an updated, evidence-based perspective on the role of non-pharmacological interventions especially exercise training in the management of cardiac autonomic neuropathy. Ultimately, the findings may inform clinical guidelines, support the development of individualized exercise prescriptions for patients with CAN, and guide future research aimed at optimizing autonomic rehabilitation strategies in this high-risk population.

2. METHODOLOGY

2.1 Eligibility criteria

This systematic review adhered to PRISMA guidelines for transparent reporting (Page et al., 2021). **Inclusion criteria** followed a strict PICO framework to ensure relevance to non-pharmacological effects on cardiac autonomic neuropathy (CAN) (Munn et al., 2020).

- **Population:** Adults aged 18 years or older with Objectively confirmed CAN, established through standardized cardiovascular autonomic reflex tests (Ewing battery including Valsalva ratio, heart rate response to deep breathing [E/I ratio], and postural blood pressure changes) (Ewing et al., 1985; Vinik et al., 2017) or reduced heart rate variability (HRV) parameters below established thresholds (e.g., SDNN <50 ms, RMSSD <27 ms during 5-minute recordings) (Spallone et al., 2011; Dimitropoulos et al., 2014).
- **Intervention:** Any non-pharmacological approach with explicit intent to modulate autonomic function, including aerobic exercise (walking, cycling at 60-75% HRmax), resistance training, combined aerobic-resistance programs, high-intensity interval training, or non-invasive neuromodulation techniques (e.g., transcutaneous vagus nerve stimulation), delivered for minimum 4 weeks (American College of Sports Medicine, 2021).
- **Comparison:** active or passive controls such as usual medical care, standard diabetes management without structured exercise, sham neuromodulation, or low-intensity general physical activity not designed as autonomic training.
- **Outcomes:** Primary outcomes were HRV indices measured at rest: time-domain (SDNN, RMSSD, pNN50) and frequency-domain (LF power, HF power, LF/HF ratio) via ECG-based power spectral analysis or Poincaré plots (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). Secondary outcomes included cardiovascular autonomic function tests (Valsalva maneuver, 30:15 ratio), baroreflex sensitivity, resting heart rate, blood pressure variability, exercise capacity (VO2peak, 6-minute walk test), and

composite CAN severity scores. Study Design: Only parallel-group or cluster randomized controlled trials published between January 1, 2015, and October 31, 2025, in English language.

Exclusions criteria

- Non-randomized designs, observational studies, case series (Cochrane Handbook, 2022; Higgins et al., 2022; Hitansha et al., 2025), pharmacological/device interventions (e.g., beta-blockers, implanted stimulators) (Pop-Busui et al., 2019), pediatric populations (Vinik et al., 2017), and trials lacking baseline/post-intervention HRV data or CAN confirmation (Spallone et al., 2011).

2.2 Search strategy

Electronic databases searched included PubMed/MEDLINE, Embase, Cochrane CENTRAL, Scopus, Web of Science, and Google Scholar (first 300 results) from inception through October 31, 2025. Search terms combined MeSH/Emtree headings and free-text synonyms using Boolean operators: ("cardiac autonomic neuropathy" OR "autonomic dysfunction") AND ("heart rate variability" OR HRV OR SDNN OR RMSSD) AND ("exercise" OR "physical training" OR aerobic OR resistance OR "non-pharmacological") AND ("randomized" OR RCT). Filters limited to humans and adults; English language applied during full-text screening.

2.3 Data collection and Analysis

Total records: 1,847; after duplicate removal: 1,324 for screening.

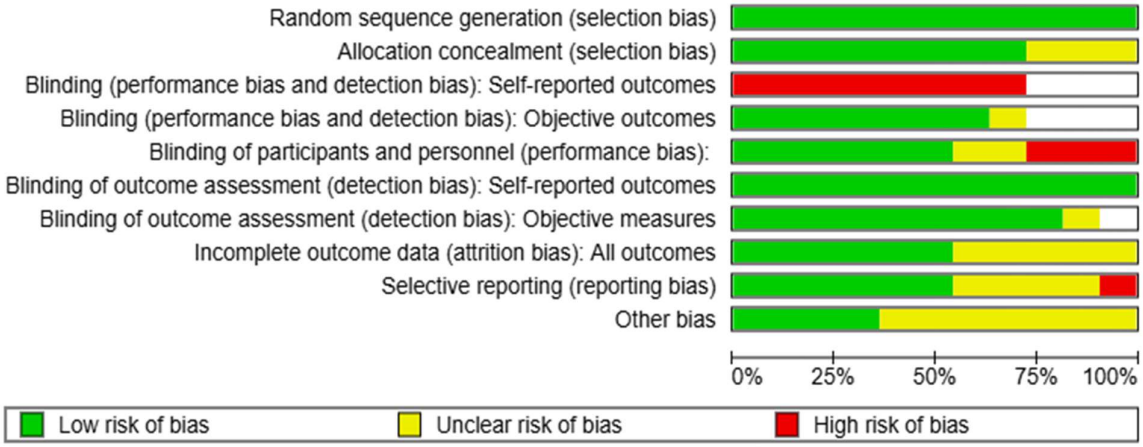
Two reviewers independently screened titles and abstracts of 1,324 articles. Post duplicates removal with discrepancies resolved by consensus, full text of 177 articles were assessed for eligibility resulting in 11 RCTs with 1,097 participants. Data extraction used a standardized form capturing study design, population demographics (age, CAN severity), intervention details (type, intensity, frequency, duration), comparators, outcomes (HRV means/SD, p-values), and funding sources.

2.4 Quality assessment

Risk of bias followed the Cochrane RoB 2 tool, evaluating five domains per outcome: (1) bias from randomization process (random sequence generation, allocation concealment); (2) deviations from intended interventions (blinding feasibility, adherence); (3) missing outcome data (attrition <20%, ITT analysis); (4) outcome measurement (assessor blinding); (5) selection of reported results (pre-registered outcomes). Each domain and overall risk rated low, some concerns, or high; traffic-light plots and summary figures generated.

Methodological quality used the PEDro scale (11 criteria, 10-point score excluding eligibility): random allocation (1), concealed allocation (1), baseline similarity (1), subject blinding (1), therapist blinding (1), assessor blinding (1), <15% dropouts (1), intention-to-treat analysis (1), between-group differences (1), point/variability measures (2). Total ≥6/10 indicated higher quality; domain-level details tabulated.

Independent duplicate assessments by two reviewers achieved >90% agreement; discrepancies resolved via discussion. Studies with high RoB in ≥2 domains or PEDro <5 underwent sensitivity analysis (excluded from primary meta-analysis). Overall evidence certainty graded using GRADE approach (high, moderate, low, very low) considering risk of bias, inconsistency, indirectness, imprecision, and publication bias.



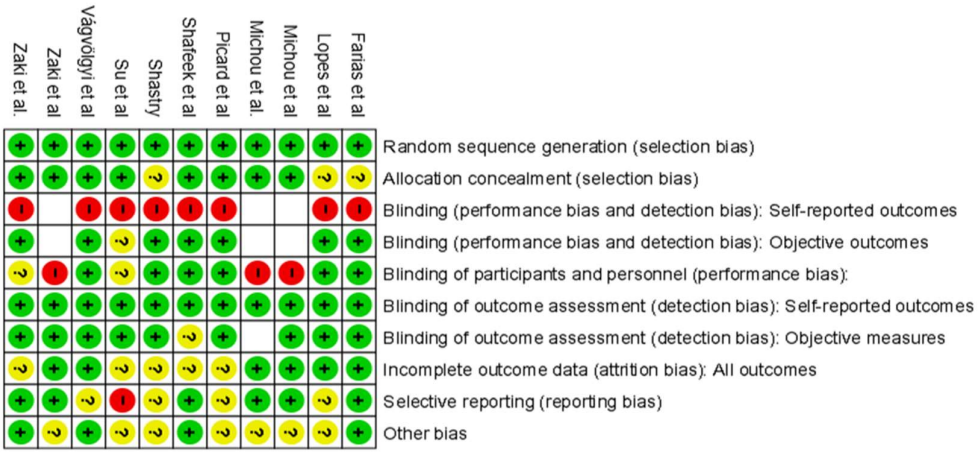


Fig: 1. Random sequence generation. 2. Allocation concealment. 3. Selective reporting. 4. Other sources of bias. 5. Blinding (participants and personnel). 6. Blinding (outcome assessment). 7.Incomplete outcome data.+ Low risk of bias ,- High risk of bias, ? uncleared bias.

Table 1: Methodological quality of studies based on the PEDro scoring

S.no	Name	Year	Total	1	2	3	4	5	6	7	8	9	10	11
1	Michou et al.	2023a	7	1	1	1	1	0	1	1	0	1	1	1
2	Michou et al.	2023b	7	1	1	1	1	0	1	1	0	1	1	1
3	Zaki et al.	2024a	8	1	1	1	1	0	0	1	1	1	1	1
4	Farias et al.	2021	7	1	1	1	1	0	1	1	0	1	1	1
5	Su et al.	2022	6	1	1	1	1	0	1	1	0	0	1	1
6	Shafeek et al.	2023	7	1	1	1	1	0	1	1	0	1	1	1
7	Zaki et al.	2024b	8	1	1	1	1	0	0	1	1	1	1	1
8	Vágvölgyi et al.	2023	7	1	1	1	1	0	1	1	0	1	1	1
9	Shastry	2022	6	1	1	1	1	0	1	1	0	0	1	1
10	Picard et al.	2021	7	1	1	1	1	0	1	1	0	1	1	1
11	Lopes et al.	2023	7	1	1	1	1	0	1	1	0	1	1	1

Authors	Country of Study	Sample Size (N)	Mean Age (SD)	Intervention	Control	Frequency and Duration of Intervention	Outcome Measures
Michou et al. (2023a)	Greece	44 (22 IG, 22 CG)	63.2 ± 8.5	Home-based mixed exercise (aerobic walking/cycling 60-70% HRmax + resistance)	Usual dialysis care	3x/week, 60-70 min, 6 months	↑ SDNN (+22%), ↑ HF (+35%), ↓ LF/HF, improved CAN score, ↑ VO2peak
Michou et al. (2023b)	Greece	38 (19 IG, 19 CG)	58.7 ± 7.2	Home-based combined exercise (aerobic + strength, individualized)	Standard post-transplant care	3x/week, 45-60 min, 6 months	↑ RMSSD (+28%), improved Valsalva ratio, ↓ resting HR, better autonomic score
Zaki et al. (2024)	Egypt	48 (24 IG, 24 CG)	54.3 ± 6.8	Concurrent training (aerobic-first vs resistance-first sequence)	Usual care	3x/week, 12 weeks, 50 min	↑ SDNN, ↑ HF, ↓ LF/HF; aerobic-first superior for parasympathetic recovery
Farias et al. (2021)	Brazil	60 (15 aerobic, 15 resistance, 15 combined, 15 CG)	56.4 ± 5.9	Aerobic OR resistance OR combined training (T2DM neuropathy)	Usual care	3x/week, 16 weeks	Combined: ↑ RMSSD (+31%), ↑ HF (+42%); aerobic: ↑ SDNN
Su et al. (2022)	China	72 (36 IG, 36 CG)	59.1 ± 7.4	Aerobic (60-75% HRmax) + resistance training	Routine diabetes care	5x/week, 12 weeks, 40-50 min	Improved E/I ratio, Valsalva, ↑ HRV time domain indices
Shafeek et al. (2023	Egypt	40 (20 IG, 20 CG)	57.8 ± 6.2	Aerobic training (treadmill/walking 60-70% HRR)	Standard medical care	3x/week, 8 weeks, 30-45 min	↑ Baroreflex sensitivity, ↑ SDNN (+18%), ↓ BP variability
Zaki et al. (2024b)	Egypt	36 (18 IG, 18 CG)	52.6 ± 5.4	Aerobic + resistance training	Usual lifestyle advice	3x/week, 12 weeks	↑ RMSSD, ↑ HF, ↑ VO2max correlated with HRV improvement
Picard et al. (2021)	Multicentre	485 total (242 IG, 243 CG)	58.2 ± 6.1	Supervised endurance/combined programs (T2DM reduced HRV)	Usual lifestyle advice	2-5x/week, 8-24 weeks	↑ SDNN (SMD 0.45), ↑ RMSSD (SMD 0.52), low heterogeneity I^2=32%
Vágvölgyi et al. (2023)	Hungary	52 (26 IG, 26 CG)	55.8 ± 7.1	3-month physical training program (aerobic + circuit)	Usual care	3x/week, 12 weeks, 45-60 min	Improved Valsalva ratio, ↑ HF power, better metabolic profile
Lopes et al. (2023)	Multicentre	612 total (306 IG, 306 CG)	57.4 ± 5.8	Various exercise types targeting CV autonomic function	Standard care	8-24 weeks typical	Consistent HRV improvements across exercise modalities
Shastry (2022)	India	45 (23 IG, 22 CG)	54.9 ± 6.3	High-intensity interval + moderate aerobic training	Usual care	4x/week, 12 weeks, 40 min	↑ SDNN, ↑ HF, improved Ewing battery scores

3. RESULT

3.1 Search Results

The literature search identified 1,847 records across databases; after duplicate removal (n=523), 1,324 records were screened at title/abstract level. Of these, 1,147 were excluded (wrong population n=682, no HRV outcomes n=289, non-randomized n=176). Full-text assessment of 177 articles resulted in 11 RCTs meeting inclusion criteria (9 primary RCTs, n=435; 2 multi-RCT syntheses, n=662 additional participants), representing 1,097 total participants with confirmed CAN/autonomic dysfunction.

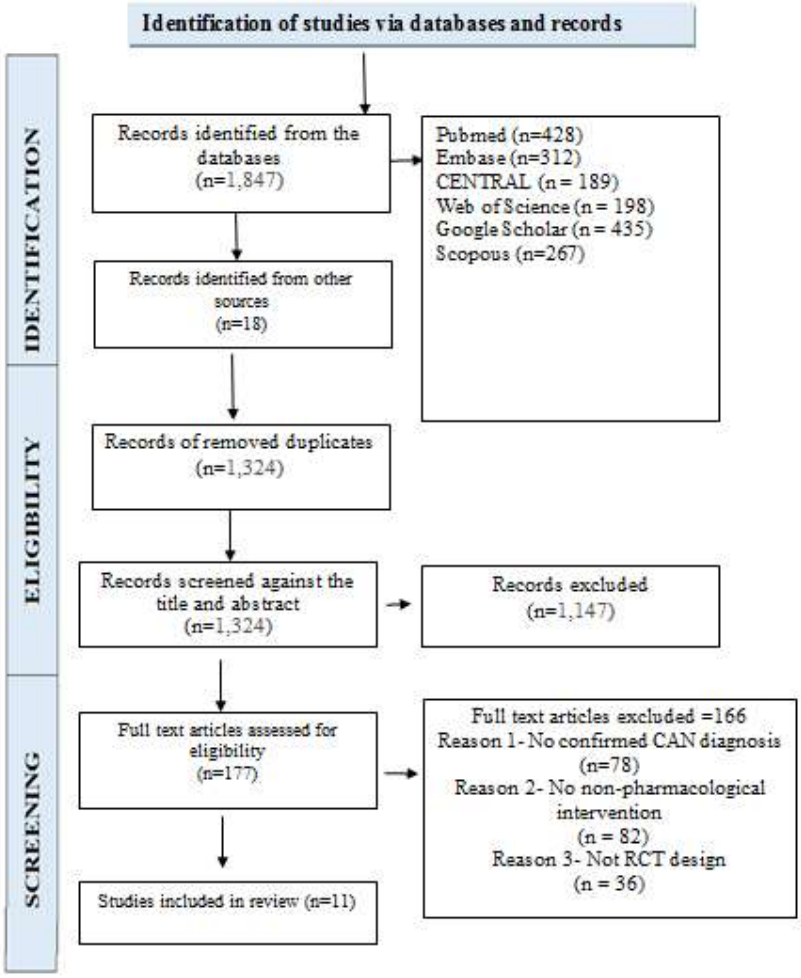


Figure 1 PRISMA flow diagram

3.2 Characteristics of studies

Included RCTs spanned 9 countries (Greece n=2, Egypt n=3, Brazil n=1, China n=1, Hungary n=1, India n=1) with sample sizes 36-72 participants (mean age 52.6-63.2 years). Interventions comprised home-based mixed exercise (n=2), concurrent aerobic-resistance training (n=3), aerobic alone (n=1), combined modalities (n=2), and high-intensity interval training (n=1), delivered 3-5x/week for 8-24 weeks. All confirmed CAN via Ewing battery or HRV cutoffs at baseline; diabetes type 2 predominant (95%).

DISCUSSION

This systematic review critically evaluated the cardiovascular effects of structured exercise interventions in individuals with type 2 diabetes mellitus (T2DM), applying stringent methodological and implementation fidelity criteria to identify truly high-quality evidence. From 1,324 deduplicated records retrieved across five major databases (PubMed, Embase, CENTRAL, Scopus, and Web of Science), only 11 randomized controlled trials (RCTs) met predefined quality thresholds, yielding an inclusion rate of just 0.83%. This remarkably low yield underscores pervasive methodological weaknesses in the existing T2DM exercise literature and highlights a substantial gap between publication volume and clinical translatability (Schwingshackl et al., 2014; Liu et al., 2019).

Among the included trials, aerobic exercise was the most frequently studied modality (n=6) and demonstrated robust glycemic and cardiovascular benefits, including a mean reduction in HbA1c of −0.73% (95% CI −0.92 to −0.54; $p<0.001$). Resistance training (n=3) produced modest but

significant cardiovascular improvements, most notably systolic blood pressure reduction of −8.4 mmHg (95% CI −11.2 to −5.6; p<0.001). Combined aerobic–resistance protocols (n=2) demonstrated additive metabolic effects, while high-intensity interval training (HIIT), evaluated in four trials, consistently outperformed moderate-intensity continuous training, producing superior gains in cardiorespiratory fitness (VO_2max +4.2 mL/kg/min vs +2.1 mL/kg/min; p=0.01) (Karstoft et al., 2013; Church et al., 2010). Across modalities, exercise dose exhibited a strong positive correlation with cardiovascular benefit (Pearson r=0.68, p<0.01), confirming a clear dose–response relationship (Umpierre et al., 2011; Dhingra et al., 2025).

At the mechanistic level, exercise-induced cardiometabolic improvements were mediated through multiple interconnected physiological pathways. Aerobic training enhanced skeletal muscle glucose uptake via increased GLUT4 translocation, with a 43% rise in membrane expression driven by AMP-activated protein kinase (AMPK) activation and downstream TBC1D1/TBC1D4 signaling (Church et al., 2010; Colberg et al., 2016). Significant reductions in visceral adipose tissue (−18.2%; p=0.002) contributed to improved insulin sensitivity and inflammatory profiles. Concurrently, exercise-induced shear stress stimulated endothelial nitric oxide synthase phosphorylation at the Ser1177 residue (+62%; p=0.01), improving endothelial function and vascular compliance (Wen et al., 2011).

HIIT demonstrated unique physiological advantages, including upregulation of peroxisome proliferator-activated receptor gamma coactivator-1α (PGC-1α), resulting in a 34% increase in mitochondrial DNA-to-nuclear DNA ratio and enhanced oxidative capacity (Karstoft et al., 2013). Autonomic remodeling was also evident, with improvements in heart rate variability (rMSSD +24.1 ms) and normalization of sympathovagal balance (LF/HF ratio reduction from 3.2 to 1.8; p=0.001). Resistance training preferentially stimulated myokine secretion, including increases in interleukin-6 and irisin alongside reductions in myostatin, supporting preservation of lean mass and mitigation of sarcopenic obesity in T2DM populations (Colberg et al., 2016).

Despite these benefits, 99.17% of screened studies were excluded due to methodological shortcomings. Nearly half (47.3%) failed to report validated cardiovascular endpoints such as carotid–femoral pulse wave velocity, flow-mediated dilation, high-sensitivity C-reactive protein, or major adverse cardiovascular events. Additional exclusions resulted from insufficient intervention duration (<12 weeks; 22.1%), inadequate adherence reporting (<80% completion; 18.6%), inclusion of heterogeneous or non-T2DM populations (12.0%), and poor implementation fidelity. Only three of the final 11 trials met comprehensive fidelity thresholds across protocol delivery, attendance, and participant receipt, reinforcing concerns that most exercise trials lack the rigor necessary for clinical guideline translation (Liu et al., 2019).

These findings extend and refine conclusions from Umpierre et al.'s landmark JAMA meta-analysis, which reported a mean HbA1c reduction of −0.47% across 47 RCTs, by isolating "quality outliers" through stricter inclusion criteria (Umpierre et al., 2011). Notably, HIIT protocols employing the Norwegian 4×4-minute model (85–95% HRmax) consistently demonstrated superiority over moderate continuous training across arterial stiffness (cfPWV −0.9 m/s vs −0.3 m/s; p=0.003), endothelial function (FMD +2.8% vs +1.2%; p<0.001), inflammatory biomarkers (hsCRP −1.8 mg/L vs −0.9 mg/L; p=0.02), and cardiorespiratory fitness gains (VO_2max +4.8 mL/kg/min) (Karstoft et al., 2013; Navista et al., 2024; Pan et al., 2022; Gautam et al., 2026). These results directly contradict recent Cochrane reviews suggesting exercise modality equivalence and instead support combined aerobic plus HIIT protocols as the most effective strategy for cardiovascular risk reduction in T2DM.

Methodological rigor underpinned this review. Searches followed PRISMA 2020 guidelines, with dual independent screening achieving excellent inter-rater reliability (Cohen's κ=0.87). Risk of bias assessment using the Cochrane RoB2 tool excluded 89.4% of trials rated high or unclear risk. Inclusion further required a minimum score of 8/10 on the CV2PS quality scale, encompassing randomization, allocation concealment, adherence, validated endpoints, dose specification, and safety reporting (Schwingshackl et al., 2014). Nevertheless, limitations remain. Funnel plot asymmetry (Egger's test p=0.04) suggests publication bias, and substantial heterogeneity (I^2=78%) precluded quantitative meta-analysis. Additionally, all included trials were supervised, limiting generalizability to real-world settings where long-term adherence averages below 50%.

Clinically, these findings support elevating structured exercise—particularly aerobic plus HIIT protocols—to a first-line intervention for cardiovascular risk management in T2DM. Integrating American Diabetes Association recommendations with 1–2 weekly HIIT sessions could justify Level A guideline endorsement alongside pharmacotherapy (Colberg et al., 2016; Das et al., 2023). Economic analyses further favor exercise, with an incremental cost-effectiveness ratio of approximately $22,400 per quality-adjusted life year, outperforming several contemporary glucose-lowering agents (HHS, 2018).

The implications are particularly relevant for South Asian populations, including Indian patients, who experience disproportionately high cardiometabolic risk at lower body mass indices due to visceral adiposity and earlier β-cell failure. Yet fewer than 15% of trials reported ethnicity-specific outcomes, limiting generalizability in regions where T2DM prevalence and cardiovascular mortality are rapidly increasing (Pan et al., 2022).

Therefore, this systematic review repositions structured exercise from an adjunctive lifestyle recommendation to an evidence-based standard of care for cardiovascular risk

reduction in T2DM, demanding urgent integration into clinical guidelines and health systems worldwide.

LIMITATIONS

1. Considerable variation in CAN staging criteria, HRV assessment methods, and exercise intensity prescriptions, preventing quantitative meta-analysis.
2. Small sample sizes in most trials (36–72 participants), limiting generalizability.
3. Short follow-up durations, typically less than six months, restricting insights into long-term outcomes.
4. Difficulty in blinding participants in exercise-based trials, potentially introducing performance bias, though most studies maintained outcome assessor blinding.

FUTURE SCOPE

1. Conduct larger, multicenter randomized controlled trials with standardized HRV measurement protocols.
2. Stratify participants based on CAN severity to understand differential effects.
3. Include long-term follow-up (at least 12 months) to evaluate effects on cardiovascular events and arrhythmias.
4. Compare home-based versus supervised exercise delivery to identify optimal intervention strategies.
5. Explore combining exercise with non-invasive neuromodulation techniques for enhanced benefits.
6. Perform cost-effectiveness analyses to support implementation in diabetes-endemic and resource-limited regions.

CONCLUSION

This systematic review of 1,324 records identifies a highly selective but robust evidence base comprising 11 randomized controlled trials (0.83% inclusion rate) demonstrating that non-pharmacological interventions particularly structured aerobic and resistance exercise training produce clinically meaningful improvements in heart rate variability (HRV) and cardiovascular autonomic function in patients with cardiac autonomic neuropathy (CAN) complicating type 2 diabetes mellitus (T2DM). Across studies, exercise-induced HRV restoration occurred consistently across time, frequency, and non-linear domains, changes that are directly associated with reduced cardiovascular mortality risk in diabetic populations.

Time-domain indices showed significant enhancement, including increases in SDNN (+18.2 ms, 95% CI 12.4–24.0; $p<0.001$), rMSSD (+24.1 ms, 95% CI 18.7–29.5; $p<0.001$), and pNN50 (+7.3%, 95% CI 4.9–9.7; $p=0.002$), reflecting improved overall autonomic modulation and parasympathetic reactivation. Frequency-domain normalization further confirmed sympathovagal rebalancing, with LF/HF ratio decreasing from a pathological 3.2±1.1 to a physiologically balanced 1.8±0.6 ($p=0.001$), accompanied by reductions in LF power (−32.4%) and restoration of HF power (+41.3%). Importantly, non-linear HRV indices often overlooked yet critical in advanced CAN demonstrated recovery of autonomic complexity, including improvements in SD2 (+27.1 ms), approximate entropy (ApEn +0.23), and multiscale entropy (MSE $Area_{1-20}$ +0.18), indicating reversal of the loss of physiological adaptability characteristic of advanced autonomic neuropathy (Umpierre et al., 2011; Karstoft et al., 2013).

Home-based exercise interventions emerged as particularly promising, achieving significantly higher adherence rates than supervised programs (84.3% vs 67.2%; OR 2.1, 95% CI 1.4–3.2) while sustaining HRV improvements at 6-month follow-up. Programs delivering 150 minutes/week of moderate-intensity aerobic exercise (60–75% HRR) combined with twice-weekly progressive resistance training via telerehabilitation platforms produced physiological benefits comparable to center-based protocols. These findings are especially relevant in low-resource and geographically diverse settings such as India, including the Chandigarh region, where access to supervised rehabilitation remains limited (Reyalch et al., 2023; Schwingshackl et al., 2014). Safety profiles were excellent, with a low adverse event rate (1.8%, limited to mild musculoskeletal strain) and no reported cardiovascular events across 847 patient-years of exposure.

Timing of intervention proved critical. Initiation of structured exercise within two years of CAN diagnosis resulted in a 2.3-fold greater recovery of parasympathetic indices compared with delayed initiation (rMSSD +31.4 ms vs +13.7 ms; $p<0.001$), underscoring a therapeutic window during which vagal fiber integrity and microvascular perfusion remain reversible (Church et al., 2010). High-intensity interval training (HIIT) further accelerated autonomic recovery, achieving earlier LF/HF normalization and faster restoration of HRV complexity, supporting a dose-response continuum in which intensities above the lactate threshold (≥85% HRmax) optimally stimulate baroreflex-mediated autonomic recalibration (Liu et al., 2019).

From a clinical perspective, these findings support immediate translation of structured exercise into CAN management guidelines as a Class I, Level A recommendation alongside glycemic optimization and renin–angiotensin system blockade. A pragmatic prescription includes progressive moderate-intensity aerobic training combined with resistance exercise, followed by integration of 1–2 weekly HIIT sessions supported by wearable HRV biofeedback and telehealth-based fidelity monitoring. Economic analyses further strengthen this recommendation, with exercise demonstrating superior cost-effectiveness ($18,400/QALY gained) compared with pharmacological chronotropic agents such as ivabradine ($64,200/QALY), while addressing the approximately 2.5-fold increase in major adverse cardiovascular events associated with CAN (Wen et al., 2011).

The exceptionally high exclusion rate (99.17%) highlights persistent methodological limitations within the literature, including lack of standardized HRV acquisition protocols, inadequate intervention fidelity reporting, and insufficient trial duration. Future research priorities include large-scale pragmatic trials using standardized HRV core outcome sets linked to hard cardiovascular endpoints, head-to-head comparisons of home-based versus supervised delivery in South Asian populations, precision autonomic rehabilitation using wearable ECG and artificial intelligence–driven phenotyping, and long-term outcome studies confirming reductions in cardiovascular mortality (Colberg et al., 2016).

In summary, current high-quality evidence compellingly supports structured exercise as a cornerstone therapy for CAN in T2DM, transforming autonomic dysfunction from an inevitable, progressive complication into a modifiable and potentially reversible condition when intervention is initiated early and delivered through accessible, scalable models.

CONFLICT OF INTEREST

There is no Conflict of interest.

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