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Physical exercise and diabetes: exploring the relationship and impact on health outcome

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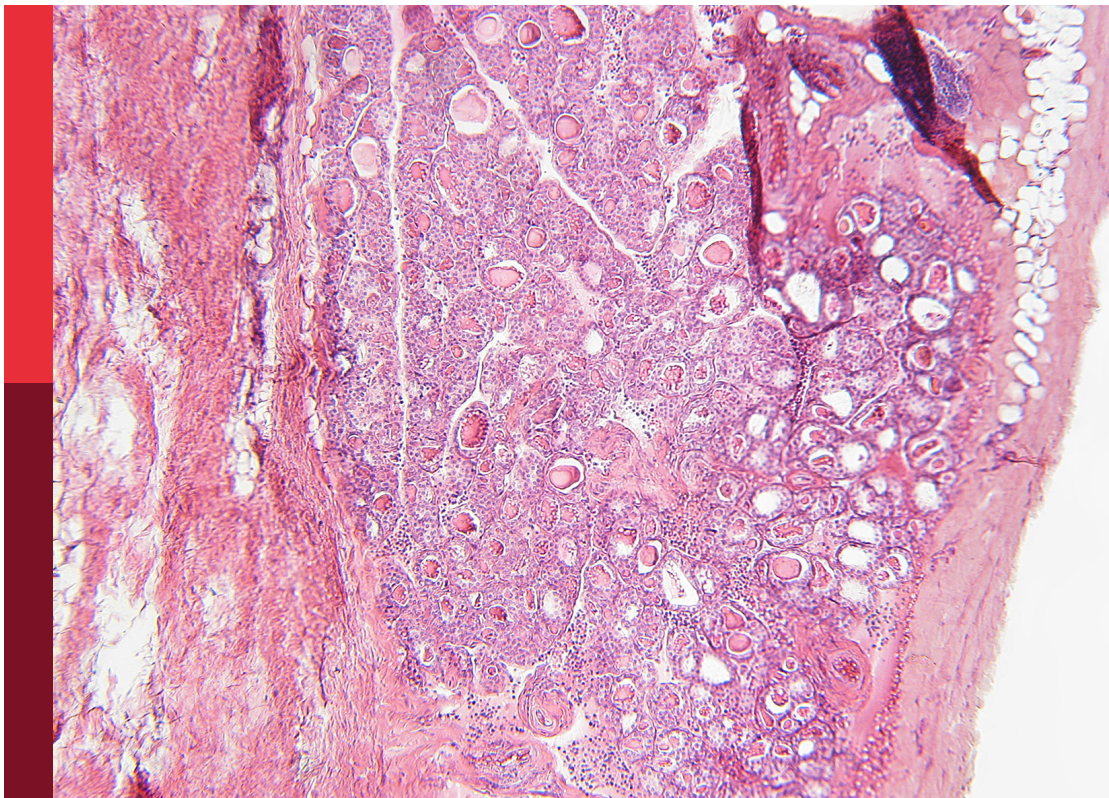

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Physical exercise and diabetes: exploring the relationship and impact on health outcome

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Editorial: Physical exercise and diabetes: exploring the relationship and impact on health outcome

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Editorial on the Research Topic
Physical exercise and diabetes: exploring the relationship and impact on health outcome

Type 2 diabetes mellitus (T2DM) has reached pandemic proportions globally, affecting over 400 million people. Beyond the well-known metabolic dysfunctions, such as impaired glucose regulation and insulin resistance, T2DM is closely linked to a plethora of comorbidities (1), result in severe long-term complications including cardiovascular disease, nonalcoholic fatty liver disease (NAFLD), stroke, neuropathy and nephropathy. Research has increasingly underscored the critical role of physical activity in managing T2DM, improving metabolic control, and enhancing overall quality of life. Recent studies have further illuminated the potential of varied exercise modalities to offer targeted benefits across different metabolic, cardiovascular, and muscular systems (2).

This Research Topic presents a collection of 10 insightful articles exploring how various forms of exercise influence the management of T2DM and its related complications, offering new avenues for treatment and rehabilitation.

A key study by Chen et al. explored the efficacy of different exercise interventions in individuals with both T2DM and a history of stroke, focusing on glycemic regulation, lipid profiles, and functional recovery. The study compared low-to-moderate intensity continuous training (LMICT), moderate-intensity interval training (MIIT), and reduced-exertion high-intensity training (REHIT) over a month-long intervention. MIIT and REHIT yielded significant improvements in glycemic control, as measured by continuous glucose monitoring (CGM) metrics, with notable reductions in glucose variability and time above target ranges. These findings align with the growing consensus that interval-based exercise protocols, particularly those involving moderate to high intensity, can be especially beneficial in reducing blood glucose fluctuations in diabetic patients. Furthermore, the REHIT group demonstrated improved functional recovery, which may offer a dual benefit in patients recovering from stroke.

The modest effects on lipid profiles seen across all exercise groups suggest that while glycemic control may be responsive to short-term interventions, longer or more targeted strategies may be needed to influence lipid metabolism. Nonetheless, the potential of MIIT and REHIT to simultaneously manage glucose variability and enhance functional outcomes is promising, particularly for complex cases involving comorbidities like stroke.

In the context of NAFLD, a common comorbidity in T2DM, Haxhi et al. investigated the effects of a counseling intervention aimed at reducing sedentary time and increasing physical activity (PA) in diabetic patients. Over a three-year period, even modest increases in moderate-to-vigorous physical activity (MVPA) were associated with significant reductions in NAFLD markers, including liver enzymes and indices of hepatic steatosis. Importantly, the intervention's success was driven not solely by achieving high levels of MVPA but by reducing sedentary time and increasing light-intensity activity.

These findings challenge the traditional emphasis on high volumes of vigorous exercise in NAFLD management and suggest that comprehensive lifestyle changes, even if modest, can positively impact liver health. For individuals with T2DM, particularly those with limited mobility or exercise capacity, this approach offers a feasible alternative to structured, high-intensity exercise regimens.

Ma et al. examined the efficacy of blood flow-restricted resistance (BFR) training compared to moderate-intensity resistance training (RT) in improving metabolic health and body composition in older adults with T2DM. Over six months, both exercise groups saw significant improvements in fasting plasma glucose (FPG), HbA1c, and blood lipid levels. Interestingly, BFR was found to be equally effective as moderate-intensity RT in enhancing these metabolic markers, despite involving lower exertion levels.

For older adults, particularly those new to exercise, BFR offers a promising alternative that minimizes strain and mechanical load while delivering similar metabolic benefits. The potential to improve muscle performance and body composition without necessitating high exertion makes BFR an attractive option for individuals with mobility issues or those recovering from injury.

The study by Yang et al. provided a comprehensive analysis of the global burden of T2DM attributable to physical inactivity. Between 1990 and 2019, mortality and disability-adjusted life years (DALYs) due to physical inactivity more than doubled. This alarming trend underscores the need for public health interventions aimed at increasing PA levels worldwide. Notably, countries with lower socioeconomic indices experienced a disproportionately higher burden of inactivity-related T2DM, highlighting the need for equitable access to exercise facilities and public health programs.

This global perspective reinforces the role of physical inactivity as a key modifiable risk factor in the prevention and management of T2DM. Addressing the disparities in PA levels across different regions and socioeconomic groups will be crucial in curbing the global diabetes epidemic.

A fascinating dimension of exercise's role in T2DM management involves its effects on inflammation. Kim et al. explored the relationship between exercise and serum polyclonal free light chains (FLCs), a biomarker of immune activation and inflammation. After nine months of aerobic, resistance, or combined exercise, T2DM patients exhibited reduced levels of FLCs, suggesting a protective effect against chronic low-grade inflammation.

Notably, this reduction in FLCs occurred regardless of exercise modality, indicating that the anti-inflammatory benefits of exercise are not modality-specific but rather a general consequence of increased PA. Given the role of chronic inflammation in the pathogenesis of T2DM and its complications, FLCs may emerge as a valuable biomarker for monitoring the effectiveness of exercise interventions in mitigating inflammatory states.

Yang et al. investigated the potential mediating role of remnant cholesterol (RC) in the relationship between PA and diabetes risk. Their findings revealed that higher levels of PA were associated with a lower risk of T2DM, with RC acting as a partial mediator. This study adds a novel layer to our understanding of how exercise impacts lipid metabolism and diabetes risk.

The identification of RC as a mediator suggests that PA may reduce T2DM risk not only through traditional mechanisms like improved insulin sensitivity but also by favorably altering lipid metabolism. This highlights the multifaceted benefits of PA in metabolic health.

Lastly, Qiu et al.'s meta-analysis examined the impact of exercise on flow-mediated dilation (FMD) in T2DM patients. High-intensity interval training (HIIT) emerged as the most effective exercise modality for improving FMD, a marker of vascular health. Frequent, shorter exercise sessions (<60 minutes) were associated with the most significant improvements in FMD.

These findings provide strong evidence for recommending HIIT as a superior strategy for enhancing vascular function in T2DM patients, potentially offering protection against cardiovascular complications.

The emerging research highlights the diverse and far-reaching benefits of exercise in managing T2DM and its associated complications. From glycemic control and lipid metabolism to inflammation and vascular health, the evidence is clear: regular physical activity, regardless of intensity or modality, plays a central role in improving outcomes for individuals with T2DM. As research continues to evolve, a personalized, multidimensional approach to exercise may emerge as the gold standard for diabetes care.

Abbreviations: BFR, blood flow-restricted resistance exercise; CGM, continuous glucose monitoring; FLCs, free light chains; FMD, flow-mediated dilation; FPG, fasting plasma glucose; HIIT, High-intensity interval training; LMICT, low-to-moderate intensity continuous training; MIIT, moderate-intensity interval training; MVPA, moderate-to-vigorous physical activity; NAFLD, nonalcoholic fatty liver disease; PA, physical activity; RC, remnant cholesterol; REHIT, reduced-exertion high-intensity training; RT, resistance training; T2DM, type 2 diabetes mellitus.

Author contributions

RC: Writing – original draft, Writing – review & editing. IC-M: Writing – original draft, Writing – review & editing. FM: Writing – original draft, Writing – review & editing.

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References

1. Codella R, Della Guardia L, Terruzzi I, Solini A, Folli F, Varoni EM, et al. Physical activity as a proxy to ameliorate inflammation in patients with type 2 diabetes and periodontal disease at high cardiovascular risk. *Nutrition Metab Cardiovasc Diseases*. (2021) 31:2199–209. doi: 10.1016/j.numecd.2021.04.022

2. Vandoni M, Calcaterra V, Carnevale Pellino V, De Silvestri A, Marin L, Zuccotti GV, et al. Fitness and fatness" in children and adolescents: an italian cross-sectional study. *Children*. (2021) 8:762. doi: 10.3390/children8090762

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Exercise training modalities in prediabetes: a systematic review and network meta-analysis

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Background: Lifestyle modification based on exercise intervention is still the primary way to delay or reverse the development of diabetes in patients with prediabetes. However, there are still challenges in setting up a detailed exercise prescription for people with prediabetes. This study mainly ranks exercise prescriptions by comparing the improvement of glucose and lipid metabolism and the level of weight loss in patients.

Method: All studies on exercise intervention in prediabetes were identified by searching five electronic databases. Risk assessment and meta-analysis were performed on eligible studies.

Results: Twenty-four studies involving 1946 patients with prediabetes and seven exercise intervention models were included in the final analysis. The meta-analysis showed that exercise of any type was more effective for glycemic control in prediabetes than no exercise. However, the changes in blood glucose were moderate. In prediabetes, combining moderate-intensity aerobic exercise with low-to moderate-load resistance training showed the most significant improvements in glycosylated hemoglobin (HbA1c), body mass index (BMI), body weight (BW), total cholesterol (TC), and low-density lipoprotein cholesterol (LDL) (P-score=0.82; 0.70; 0.87; 1; 0.99), low-to moderate-load resistance training showed the most significant improvements in fasting blood glucose (FBG) (P-score=0.98), the vigorous-intensity aerobic exercise showed the most significant improvements in 2-hour post-meal blood glucose (2hPG) and systolic blood pressure (SBP) (P-score=0.79; 0.78), and moderate-intensity aerobic exercise showed the most significant improvements in diastolic blood pressure (DBP) (P-score=0.78).

Conclusion: In summary, moderate-intensity aerobic exercise, low-to moderate-load resistance training and the combination of both have beneficial effects on glycemic control, weight loss, and cardiovascular health in patients with prediabetes. These findings provide valuable guidance for rehabilitation clinicians and patients alike to follow.

Systematic review registration: https://www.crd.york.ac.uk/PROSPERO/, identifier CRD 42021284922.

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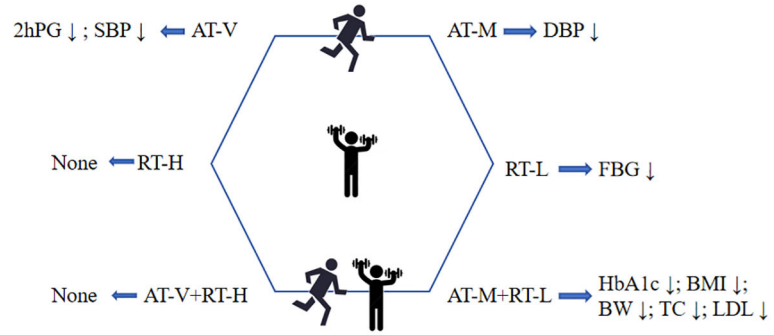
KEYWORDS

exercise, prediabetic state, glycemic control, weight loss, cardiovascular risk factors, network meta-analysis



glycosylated hemoglobin(HbA1c), fasting blood glucose (FBG) , 2-hour post-meal plasma glucose (2hPG), body weight (BW), body mess index(BMI), total cholesterol (TC), low-density lipoprotein cholesterol (LDL), diastolic blood pressure (DBP) , systolic blood pressure (SBP).

AT-V (vigorous-intensity aerobic exercise), AT-M (moderate-intensity aerobic exercise), RT-H (high-load resistance training), RT-L (low-to moderate-load resistance training), AT-V+RT-H (combined vigorous-intensity aerobic exercise with high-load resistance training), AT-M+RT-L (combined moderate-intensity aerobic exercise with low-to moderate-load resistance training)

GRAPHICAL ABSTRACT

Key points

In this network meta-analysis, we report that for prediabetes, moderate-intensity aerobic exercise combined with low-to moderate-load resistance training, moderate-intensity aerobic exercise, and low-to moderate-load resistance training should be considered the top three exercise interventions for improving glycemic control, weight control, and cardiovascular risk factors.

Specifically, moderate-intensity aerobic exercise combined with low-to moderate-load resistance training showed the best results in reducing glycosylated hemoglobin (HbA1c), body mass index (BMI), body weight (BW), total cholesterol (TC) and low-density lipoprotein cholesterol (LDL); and low- to moderate-load resistance training was more effective at improving fasting blood glucose (FBG) than moderate-intensity aerobic exercise combined with low-to moderate-load resistance training. In addition, vigorous-intensity aerobic exercise significantly reduced systolic blood pressure (SBP) and 2-hour post-meal blood glucose (2hPG).

In the subgroup analysis, we found that FBG reduction was more significant in patients older than 60. Moreover, improvements in HbA1c, TC and BMI increased with training time, but the optimal intensity and type of exercise remained moderate-intensity aerobic exercise combined with low-to moderate-intensity resistance training.

1 Background

Prediabetes is a high-risk state for diabetes, usually comprising impaired fasting glucose (IFG), impaired glucose tolerance (IGT), or both (CGI). It is also defined as a blood glucose indicator above normal but below the threshold for diabetes. Genetic factors, physical inactivity, and shifts in the structure of diets, including high in sugar, fat and low in dietary fiber, have increased the prevalence of prediabetes globally, and experts predict that by 2030, more than 470 million people will have prediabetes (1, 2).

It has been reported that 5%~10% of prediabetes develops into diabetes each year and up to 70% of prediabetes eventually develops into diabetes (3, 4). In addition to the ultra-high rate of diabetes conversion, prediabetes is also associated with an increased risk of early and chronic kidney disease, autonomic neuropathy, and cardiovascular disease (5). Therefore, as the prime time to interrupt type 2 diabetes, prediabetes should be subject to early intervention to avoid the potential effects of prediabetes itself and to prevent it from developing into diabetes or to mitigate some of the potential consequences of developing diabetes.

Current studies have all demonstrated that lifestyle modification and pharmacological interventions play a significant role in delaying the progression of prediabetes to diabetes. In terms of the effectiveness of interventions for prediabetes, medications such as metformin and acarbose are less effective than lifestyle

enhancement. Moreover, the choice of pharmacological interventions appears to put patients at higher risk and financial stress. Therefore, lifestyle is currently the intervention of choice for prediabetes (6, 7). As an essential component of lifestyle interventions, exercise interventions have been shown to aid the benign regression of prediabetes by improving insulin resistance, blood glucose levels, lipid metabolism, inflammatory response, and gut flora.

Current guidelines recommend that moderate intensity aerobic exercise is preferred in prediabetes, supplemented by resistance training, when possible, but do not recommend at an appropriate intensity. Aerobic, resistance, and combination training are now widely used in the prediabetic population. A comprehensive comparison of these intervention types has been made, recommending aerobic and combination exercise as the best type of exercise for the prediabetic population (8). However, exploring the benefits of exercise beyond exercise intensity has many limitations and risks, and vague recommendations for exercise prescription are often not understood by patients, which also makes exercise difficult to maximize treatment effects. Therefore, based on the complete concept of exercise prescription setting, this study comprehensively considered four aspects of exercise type, exercise frequency, exercise intensity, and exercise time, and conducted a network meta-analysis of exercise intervention modalities for prediabetes to (I) evaluate the comparative effects of different exercise prescriptions on weight loss, glycemic regulation and, cardiovascular fitness in prediabetes, (II)to contribute to the development of a hierarchy of exercise interventions for prediabetes.

2 Methods

This work was conducted by Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Network Meta-Analyses (PRISMA-NMA) (9). In addition, this study has been registered with PROSPERO, under CRD42021284922. The PRISMA Checklist and Protocol were presented in Additional File 1: Appendix 1, 2.

2.1 Search strategy

We searched PubMed, Embase, Web of Science, Cochrane Library, and Sport Discus for relevant studies from their inception dating to October 2022. The search strategy was constructed around the PICOS tool: (P) Participants: patients with prediabetes; (I) Intervention: Detailed exercise prescription interventions; (C) Comparisons: other exercise prescription or no exercise control; (O) Outcomes: fasting blood glucose (FBG), 2-hour post-meal blood glucose (2hPG), glycosylated hemoglobin (HbA1c), body weight (BW), etc.; (S) Study type: RCTs. A complete list of the search terms is shown in Additional File 1: Appendix 3. In addition, we scanned the references of the included articles to find those that met the inclusion criteria. HZ screened and identified the results of the research to exclude duplicate records. Yt G and HZ independently screened the titles and abstracts of the remaining studies against inclusion and exclusion criteria. HZ and Yt G independently screened the full-text articles with a "yes, unsure, or no" approach. A kappa statistic was used to calculate the level of agreement between Yt G and HZ for both abstracts and full-text screening (10). A Kappa value between 0.40 and 0.59 was considered a fair agreement, 0.60 to 0.74 as a good agreement, and greater than 0.75 as an excellent agreement (11). Any disagreements that arose during this process were negotiated by the broader team.

2.2 Inclusion and exclusion criteria

2.2.1 The inclusion criteria were performed as follows

Type of participants: We included studies enrolling participants with prediabetes aged ≥18 years, excluding patients with other chronic diseases, children, adolescents, or pregnant women. Patients diagnosed with prediabetes according to the ADA (American Diabetes Association) and WHO (World Health Organization) criteria: FBG:100~125mg/dL or HbA1c 5.7% to 6.4%.

Currently, there has yet to be a consensus on the diagnostic criteria for prediabetes. According to the ADA practice standards, prediabetes is defined as FBG 100-125 mg/dL (5.6-6.9 mmol/L) or HbA1c 5.7-6.4% (39-46 mmol/mol), while the WHO defines it as an FBG of 110 to 125 mg/dL. Furthermore, the critical levels of HbA1c differed between the guidelines. The results of a large 10-year community-based prospective cohort study in the United States showed that HbA1c 5.7% to 6.4% had reasonable diagnostic specificity and had a substantial predictive value for the risk of cardiovascular events and mortality (12). Criteria for the diagnostic use of prediabetes in adults (Table 1).

Type of interventions: We focused on the following 7 exercise training modalities, and each category was designed according to the principles of frequency, intensity, duration, and type of exercise prescription and American College of Sports Medicine (ACSM) estimates of cardio and resistance exercise intensity: AT-V (vigorous-intensity aerobic exercise), AT-M (moderate-intensity aerobic exercise), RT-H (high-load resistance training), RT-L (low-to moderate-load resistance training), AT-V+RT-H (combined vigorous-intensity aerobic exercise with high-load resistance training), AT-M+RT-L (combined moderate-intensity aerobic exercise with low-to moderate-load resistance training) and CON (no exercise). The definition of each intervention is shown in Additional File 1: Appendix 4.

Type of outcomes: Outcomes of interest included glycemic control [including glycosylated hemoglobin (HbA1c), fasting

TABLE 1 Criteria for the diagnostic use of prediabetes in adults.

	IFG	IGT	CGI
FBG (mmol/L)	6.1~7.0	<6.1	6.1~7.0
2h-PG (mmol/L)	<7.8	7.8~11.1	7.8~11.1
HbA1c (%)	5.7~6.4		

blood glucose (FBG) and 2-hour post-meal plasma glucose (2hPG)], weight loss [including body weight (BW) and body mass index (BMI)] and cardiovascular risk factors [including total cholesterol (TC), low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL), diastolic blood pressure (DBP) and systolic blood pressure (SBP)].

Type of design: Randomized controlled trials (RCTs).

2.2.2 The exclusion criteria were performed as follows

(1) non-randomized design; (2) in regard to RCTs with repeated publications or apparent duplication of data, only one study with more complete data was kept; (3) means and standard deviations were unavailability in the results, and authors did not reply to our requests for data; (4) vague descriptions of exercise modalities; (5) full text of the study could not be available through relevant databases and other means.

2.3 Data extraction

Relevant publication information; (1) number; (2) author; (3) year of publication; (4) country; (5) sample size; (6) mean age; (7) the details of exercise prescription were recorded using the FITT principle (frequency, type, time and intensity); (8) outcomes (FBG, 2hPG, HbA1c, Weight, BMI, TC, LDL, HDL, SBP, DBP). If the original study reported a standard error in the experimental and control groups, the standard deviation was calculated by the formula: standard deviation (SD) = standard error (SE) $\times \sqrt{N}$. If both were missing, we would estimate SD based on the confidence interval, t-value, quartile, range, or p-values as described in section 7.7.3 of the Cochrane Handbook for Systematic Reviews.

2.4 Risk of bias assessment

HZ and Yt G independently assessed the risk of included studies based on the bias 2.0 Tool (37). Examined domains; (1) randomization process; (2) deviations from the intended interventions; (3) missing outcome data; (4) measurement of the outcome; (5) selection of the reported results.

2.5 Statistical analysis

The net Meta package of R3.6.3 software was applied to perform an NMA combining direct and indirect comparisons based on the Frequentist model (38, 39). Arm-level data was imported into the R software in CSV format. Allowing for the consistent rating scales or units of each outcome, the mean difference (MD) was chosen to measure the effect sizes. The effect sizes were then synthesized using a random-effects NMA model. We presented the summary MD, 95% credible intervals (CrIs) for all pairwise comparisons in the league table. Furthermore, we showed the results of comparison of each exercise modality and control group in the form of a forest plot. Besides, we used p-score to rank exercise modalities based on the improvement of glucose and lipid metabolism and the level of weight loss (40). A higher p-score indicates a greater degree of improvement. For different clinical trials, it is necessary to ensure the consistency of their baseline levels. Therefore, prior to analysis of the results, we evaluated the transitivity assumption by comparing the distribution of potential effect modalities (year of publication, sample size, mean age, percentage of male) (Additional File 1: Appendix 5) across the studies. Tau square (τ^2) test and p-value were used to qualitatively analyze the statistical heterogeneity between the studies. Larger $\tau 2$ and smaller p-value indicate greater possibility of heterogeneity. Moreover, I^2 is a parameter for quantitative analysis of the heterogeneity between all results. I^2 < 25% means low heterogeneity; 25%-50% means moderate heterogeneity; I^2 > 75% means high heterogeneity. We also used global and local methods to test the inconsistency of these results. Design-by-treatment test was used to evaluate inconsistency statistically for global inconsistency and separate indirect from direct evidence (SIDE test) for local inconsistency (41, 42). The potential sources of heterogeneity (publish year, mean age, percentage of males, sample size, exercise period, exercise frequency, the single session of exercise) were explored by network meta-regression through the R3.6.3 gemtc package. Subgroup analysis was performed by the forest spot package of R3.6.3 software. In addition, the adjusted funnel plot was compared to assess the risk of publication bias under specific circumstances. Egger's test suggests publication bias when p< 0.05.

3 Results

A total of 4553 studies were identified according to the search strategy. After initially identifying titles and abstracts, the remaining 168 studies were screened for full text. The inter-rater reliability between the two reviewers for both abstract screening (K=0.74) and full-text screening (K=0.71) was considered good. Finally, 24 studies with 1946 participants were included in this study (Figure 1). The studies were conducted in America (n=6), China (n=6), Iran (n=1), Finland (n=4), Sweden (n=2), Chile (n=1), Netherlands (n=1), Germany (n=1), Austria (n=1) and Canada (n=1). Furthermore, in 24 studies, 8 with 3 arms, 14 with 2 arms, and 2 with 4 arms. 2 of the studies looked only at women, 2 at men, and the remaining 22 included both men and women (Table 2).

In terms of exercise categories, 234 participants (12.02%) were included in the AT-V category, 630 participants (32.37%) in the AT-M, 63 participants (3.24%) in RT-H, 226 participants (11.61%) in RT-L, 10 participants (0.51%) in the AT-V+RT-H and 63 participants (3.24%) in the AT-M+RT-L. The remaining 720 participants were controls (no exercise). Intensity, duration, and

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TABLE 2 Characteristic of included studies.

Author Year	country	Sample Size (men)	Age (Mean ± SD)	Exercise Prescription	Results
Tahereh 2019 (13)	Iran	AT-M:136 (59) CON:136 (51)	AT-M:51.3 ± 11.2 CON:53.6 ± 9.4	AT-M:60%~70%VO_{2max},50min/day,3times/week,16weeks	a,d,e
Yan J 2019 (14)	China	AT-M:35 (10) RT-L:35 (15) CON:35 (15)	AT-M:64.23 ± 5.75 RT-L:62.06 ± 8.11 CON:60.31 ± 7.56	AT-M:60%~70%HR_{max}, 50min/day, 3times/week,12weeks RT-L:60%1RM,50min/day, 3times/week,12weeks	a,b,c,e,f,g,h
Dai X 2019 (15)	China	AT-M:34 RT-L:31 AT-M+RT-L:37 CON:35	AT-M:51 ± 5 CON:58 ± 3	AT-M:60%~70%HRmax,60min/day, 3times/week,2years RT-L:60%~80%1RM,60min/day, 3times/week,2years AT-M+RT-L:combined AT-M with RT-L	a, b,c,d,f,g,h
Kramer 2018 (16)	USA	AT-M: 88 (30) CON: 46 (14)	AT: -M:62.8 ± 12.1 CON:61.9 ± 11.9	AT-M:60%~70%HRmax,50min/day,3times/week,18months	a,c,d,e,f,g,h,i,j
Slentz 2016 (17)	USA	AT-M: 40 (17) AT-V: 38 (15)	AT-M:61.4 ± 7.1 AT-V:60.4 ± 7.0	AT-M: 50%$VO_{2reserve}$, 30 min/day, 3 times/week,6 months AT-V: 75% $VO_{2reserve}$, 60 min/day, 3 times/week,6 months	a,b,d,f,g,h
Gidlund 2016 (18)	Finland	RT-L: 20 (20) AT-M: 18 (18) CON:17 (17)	RT-L:54 ± 6.2 AT-M:56 ± 5.6 CON:54 ± 6.9	RT-L:50%1RM,60min/day,3times/week,12weeks AT-M:55%~75%HRR,60min/day,3times/week,12weeks	b,c
Liao 2015 (19)	China	AT-M:60 (33) CON:60 (35)	AT-M:42.4 ± 5.8 CON:44.1 ± 6.6	AT-M:60%~70%HRmax,30min/day,5times/week,12weeks	a,c,e,f,g,h,i,j
Herrzig 2014 (20)	Finland	AT-M:33 (9) CON:35 (9)	AT-M:58.1 ± 9.9 CON:59.5 ± 10.8	AT-M:60%~70%HRmax,60min/day,3times/week,12weeks	a,b,d,e,f,g,h, i,j
Venojarvi 2013 (21)	Finland	AT-V:39 (39) RT-H:36 (36) CON:40 (40)	AT-V:55 ± 6.2 RT-H:54 ± 6.1 CON:54 ± 7.2	AT-V:65%~75%HRR,60min/day, 3times/week,12weeks RT-H:75%~85%1RM,60min/day, 3times/week,12weeks	a,b,c,d,f,g,h, i,j
Fritz 2013 (22)	Sweden	AT-M:14 (5) CON:21 (10)	AT-M:59.1 ± 6.2 CON:61.8 ± 3.4	AT-M:60%~70%HRmax,60min/day, 5times/week,16weeks	a,b,c,d,e,f,g,h, i,j
Hansen 2012 (23)	Sweden	RT-H:9 (2) RT-L:9 (2) CON:9 (2)	RT-H:59.1 ± 6.2 RT-L:61.8 ± 3.4 CON:56.1 ± 4.4	RT-H:85%1RM,60min/day, 3times/week,16weeks RT-L:65%1RM,60min/day, 3times/week,16weeks	a,b
Alvarez 2012 (24)	Chile	AT-V:12 (0) RT-H:8 (0) AT-V+RT-H:10 (0) Con:13 (0)	AT-V:39.2 ± 9.5 RT-H:33.9 ± 9.3 AT-V+RT-H:43.3 ±8.1 CON:40.1 ± 11.4	AT-V:75%VO2max,50min/day,3times/week,22weeks RT-H:75%~85%1RM,60min/day, 3times/week,22weeks AT-V+RT-H: combined AT-V with RT-H	a,d,e,i,j
Burtscher 2009 (25)	Austria	AT-M+RT-L: 18 (8) CON: 18 (8)	AT-M+RT-L:55.8 ± 5.5 CON:59.1 ± 7.8	AT-M+RT-L:70%HRmax+70%1RM,60min/day, 3times/week,12months	a,d,e,f,g,i,j
Desch 2010 (26)	Germany	AT-V:14 (11) CON: 12 (8)	AT-V:62.3 ± 6.2 CON:62.3 ± 6.5	AT-V:75%VO2max,90min/day,3times/week,6months	a,b,c,e
Eriksson 1998 (27)	Finland	AT-M:7(3) RT-L:7(4) CON:8(8)	AT-M:60 ± 5 RT-L:40 ± 3 CON:60 ± 5	AT-M:60%VO2max,60min/day,3times/week,10weeks RT-L:50%~60%1RM,60min/day,3times/week,10weeks	a,e,f,g,i,j
Malin 2012 (28)	USA	AT-M+RT-L: 8 (3) CON: 8 (2)	AT-M+RT-L:45.4 ± 8.0 CON:49.8 ± 10.9	AT-M+RT-L:70%HRmax+70%1RM,60~70min/ day,3times/week,12weeks	a,d
Marcell 2005 (29)	USA	AT-V:20 AT-M:17 CON:14	AT-V:47.2 ± 9.2 AT-M:44.4 ± 6.5 CON:44.1 ± 9.5	AT-V:80%~90%VO_2max,30min/day,5times/week,16weeks AT-M:3.5MET,30min/day,5times/week,16weeks	d
Marcus 2009 (30)	USA	RT-H:10 (0) CON:6 (0)	RT-H:56.3 ± 6.4 CON:53.2 ± 6.5	RT-H:85%1RM,30min/day,3times/week,12weeks	a
Roumen 2008 (31)	Dutch	AT-V:54 (30) CON: 52 (28)	AT-V:58.4 ± 6.8 CON:54.2 ± 5.8	AT-V:70%VO2max,30min/day,3times/week,3years	b,c,d,e,f,g,h, i,j
Rowan 2017 (32)	Canada	AT-M:10 AT-V:11	AT-M:47.7 ± 6.93 AT-V:53.6 ± 8.21	AT-M:60%~70%HRR,30min/day,3times/week,12weeks AT-V:90%HRR,30min/day,3times/week,12weeks	a,b,e

(Continued)

TABLE 2 Continued

Author Year	country	Sample Size (men)	Age (Mean ± SD)	Exercise Prescription	Results
Yuan 2020 (33)	China	AT-M:83 (24) RT-L:82 (30) Con:83 (33)	AT-M:60.93 ± 5.71 RT-L:59.91 ± 5.92 CON:60.73 ± 5.83	AT-M:60%~70%HRmax,60min/day,3times/week,6months RT-L:50%~60~1RM,60min/day,3times/week,6months	a,b,c,d,e,f,g,i,j
sulin 2017 (34)	China	AT-V:29 (6) Con:29 (7)	AT-V:59 ± 4.4 CON:60 ± 3.4	AT-V:60%~75%VO2max,60min/day,3times/week,6months	a,b,c,d
Lin 2021 (35)	China	AT-M:43 (3) RT-L:42 (4) CON:43 (4)	AT-M:60.35 ± 4.29 RT-L:60.12 ± 3.97 CON:59.94 ± 4.40	AT-M:60%~70%HRmax,50min/day,3times/week,12months RT-L:60%~80%1RM,50min/day,3times/week,12months	a,b,c
Nicole 2019 (36)	USA	AT-V:17 AT-M:12	AT-V:45.7 ± 4.4 AT-M:50.8 ± 4.4	AT-V:79.8 ± 3.3%HRmax,60min/day,3times/week,16weeks AT-M:53.1 ± 2.3%HRR,60min/day,3times/week,16weeks	a,c,d,e,i,j

AT-M, Aerobic training of moderate intensity; AT-V, Aerobic training of vigorous intensity; RT-L, Resistance training of low to moderate load; RT-H, Resistance training of high load; AT-V +RT-H, Combined vigorous intensity aerobic exercise with high load resistance training; AT-M+RT-L, Combined moderate intensity aerobic exercise with low to moderate load resistance training; CON, Control; VO2max, Maximal Oxygen Consumption; HRmax, Maximal Heart Rate; HRR, Heart rate reserve; 1RM, one-repetition maximum; MET, Metabolic equivalent of energy; a, FBG; b, 2hPG; c, HbA1c; d, Weight; e, BMI; f, TC; g, SBP; h, DBP; i, HDL; j, LDL.

frequency of exercise interventions were reported in all studies, 23 of which lasted more than 12 weeks, 1 of which lasted 10 weeks, and all of which had a frequency of ≥ 3 times per week.

3.1 Risk of bias assessment

The summary data of ROBs assessment were presented in Figure 2 and the ROBs assessments for each study were presented in Additional File 1: Appendix 6. Overall, there were no high-risk studies here.

3.2 Network meta-analysis

3.2.1 Glycemic control

22 studies (91.6%) with 1761 patients (90.5%) assessed FBG and were eligible for NMA (Figure 3). Compared to no exercise, low-to moderate-load resistance training (-0.48mmol/L,95%CI: -0.65mmol/L~-0.32mmol/L), moderate-intensity aerobic exercise (-0.38mmol/L,95%CI: -0.51mmol/L~-0.25mmol/L), combined low-to moderate-load resistance training with moderate-intensity aerobic exercise (-0.44mmol/L,95%Cl:-0.67mmol/L~-0.21mmol/L) and vigorous-intensity aerobic exercise (-0.31mmol/L,95%Cl:-

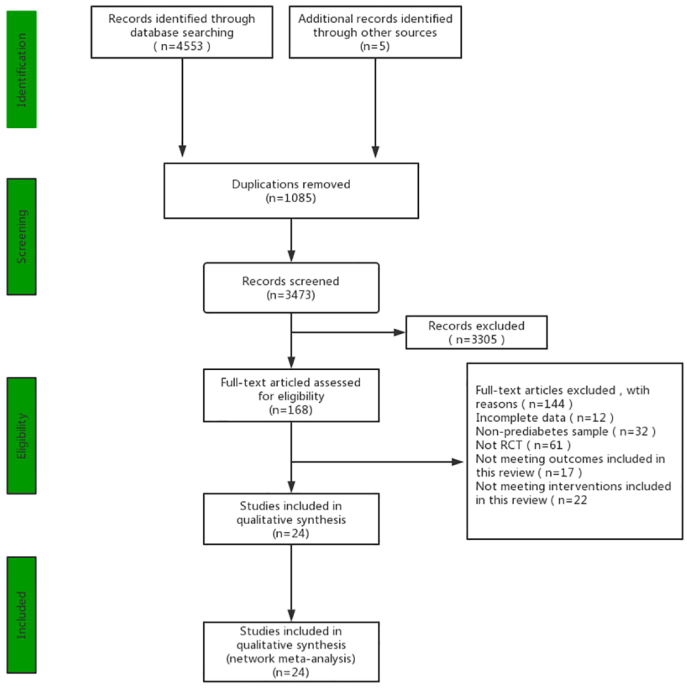

FIGURE 1
PRISMA Flow diagram of the search process for studies.

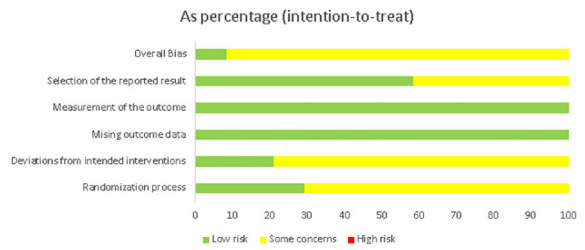

FIGURE 2
Summary of the risk of bias assessment in the individual domains of the included studies.

0.51mmol/L~-0.11mmol/L) showed significant reduction in FBG (Additional File 1: Appendix 7). Furthermore, low-to moderate-load resistance training showed the greatest potential as the best intervention to improve FBG. (P-sore=0.98, Additional File 1: Appendix 7). The result of Quantifying heterogeneity showed that I^2 was 64.2% (moderate to high) (Additional File 1: Appendix 8. There was no significant inconsistency between direct and indirect evidence (P=0.32, Additional File 1: Appendix 9.

13 studies (54.1%) with 1247 patients (64.08%) assessed HbA1c and were eligible for NMA (Additional File 1: Appendix 7). Similar to the effects on FBG, compared to no exercise, combining low-to moderate-load resistance training with moderate-intensity aerobic exercise (-0.30, 95%Cl: -0.50~-0.10), low-to moderate-load resistance training (-0.24, 95%Cl: -0.33~-0.16), moderate-intensity aerobic exercise (-0.25, 95%Cl:-0.32~-0.17) and vigorous-intensity aerobic exercise (-0.18, 95%Cl:-0.29~-0.07) showed a significant reduction in HbA1c, and ranking probability showed that combining low-to moderate-load resistance training with moderate-intensity aerobic exercise had the most significant ability to reduce HbA1c (P-score=0.82, Additional File 1: Appendix 7). The result of Quantifying heterogeneity showed that I^2 was 31.6% (moderate) (Additional File 1: Appendix 8).

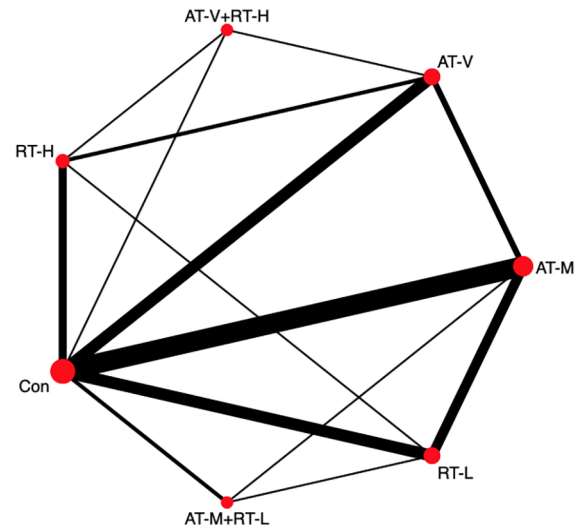

FIGURE 3
Network plot of FBG.

Notably, most prediabetes shows an increase in blood glucose 2 hours after meals, which is also a marker of impaired glucose tolerance in prediabetes. 22 studies (91.6%) with 1761 patients (90.5%) assessed 2hPG and were eligible for NMA. Compared to no exercise, vigorous-intensity aerobic exercise (-0.78mmol/L, 95%Cl: -1.40mmol/L~-0.15mmol/L) and moderate-intensity aerobic exercise (-0.53mmol/L, 95%Cl: -0.88mmol/L~-0.18mmol/L) showed a significant reduction in 2hPG. Furthermore, vigorous-intensity aerobic exercise showed the greatest potential as the best intervention to improve 2hPG (P-score=0.71, Additional File 1: Appendix 7).

3.2.2 Weight loss

15 studies (62.5%) with 1371 patients (70.45%) assessed weight loss and were eligible for NMA. Compared to no exercise, combining moderate-intensity aerobic exercise with low-to moderate-load resistance training (-3.72kg, 95%Cl: -6.34kg~-1.09kg), moderate-intensity aerobic exercise (-2.66kg, 95%Cl: -3.92kg~-1.40kg), and vigorous-intensity aerobic exercise (-2.23kg, 95%Cl: -3.62kg~-0.83kg) showed greater weight loss (Additional File 1: Appendix 7). In addition, combining moderate-intensity aerobic exercise with low-to moderate-load resistance training showed the most significant effectiveness in weight loss (P-score=0.87, Additional File 1: Appendix 7).

14 studies (58.3%) with 1214 patients (62.4%) assessed BMI and were eligible for NMA. Different from the weight loss, compared to no exercise, moderate-intensity aerobic exercise (-0.71, 95%Cl: -1.00~-0.42), and low-to moderate-load resistance training (-0.61,95%Cl: -0.97, -0.25) showed greater BMI changes (Additional File 1: Appendix 7).

3.2.3 Cardiovascular risk factors

The Framingham Risk Score (FRS) assesses the risk of cardiovascular disease (CVD). The FRS method includes gender, age, TC, LDL, HDL, SBP and smoking status as risk factors. Therefore, TC, LDL, HDL and SBP were also selected as reference factors for the risk of developing cardiovascular disease. 12 studies with 1162 patients assessed TC, 10 with 1105 patients assessed LDL, and 12 with 1170 patients assessed SBP and DBP. And We did NMA of these except HDL due to an imbalance in the baseline.

Compared to no exercise, combining moderate-intensity aerobic exercise with low-to moderate-load resistance training (TC:-0.80mmol/L, 95%Cl: -1.13mmol/L~-0.46mmol/L; LDL: -0.62mmol/L, 95%Cl: -0.93mmol/L~-0.30mmol/L), moderate-intensity aerobic exercise (TC: -0.34mmol/L, 95%Cl: -0.49mmol/L~-0.19mmol/L; SBP: -5.18mmHg, 95%Cl: -8.05mmHg~-2.31mmHg; DBP: -3.43mmHg, 95%Cl: -5.39mmHg~-1.46mmHg), vigorous-intensity aerobic exercise (TC: -0.33mmol/L, 95%Cl: -0.56mmol/L~-0.11mmol/L; SBP: -7.54mmHg, 95%Cl: -11.61mmHg~-3.47mmHg), and low-to moderate-load resistance training (TC: -0.34mmol/L, 95%Cl: -0.54mmol/L~-0.15mmol/L; SBP: -5.39mmHg,95%Cl:-10.15mmHg~-0.64mmHg; LDL:-0.29mmol/L,95%Cl:-0.48mmol/L~-0.10mmol/L) showed better improvement in TC, LDL, SBP, and DBP. (Additional File 1: Appendix 7).

Combining moderate-intensity aerobic exercise with low-to moderate-load resistance training showed the most significant improvements in TC and LDL (P-score=1.00, 0.99 respectively,

Additional File 1: Appendix 7), the vigorous-intensity aerobic exercise showed the most significant improvements in SBP (P-score=0.78, Additional File 1: Appendix 7), and moderate-intensity aerobic exercise showed the most significant improvements in DBP (P-score=0.74, Additional File 1: Appendix 7).

3.3 Meta-regression and subgroups analysis

Since our results had moderate to high heterogeneity, we performed a meta-regression of the sources of heterogeneity (year of publication, mean age, percentage of males, sample size, exercise period, exercise frequency, and the single session) on all outcomes. We found that mean age might significantly affect FBG, the sample size might affect 2hPG, and the exercise period might affect HbA1c, BMI, and TC (Additional File 1: Appendix 10), so we performed a subgroup analysis of the above. Results showed that FBG tends to be significantly reduced in elderly over 60 years, and the reduction of HbA1c, BMI, and TC tended to be greater in longer exercise period (Additional File 1: Appendix 11). In addition, we re-analyzed all results after adjusting all potential sources of heterogeneity to the median value, and the results after re-analysis did not conflict with our conclusions either (Additional File 1: Appendix 10 Finally, our comparison-adjusted funnel plot had good symmetry for all outcomes, and the results of Egger's test (FBG=0.775; 2hPG=0.440; HbA1c=0.218; BMI=0.974; Weight=0.966; TC=0.751; SBP=0.749; DBP=0.943; LDL=0.880) showed that no small study effect were found (Additional File 1: Appendix 12). Overall, the stability of our key findings was not a source of concern.

4 Discussion

4.1 Summary of evidence

This systematic review and meta-analysis revealed that combining moderate-intensity aerobic exercise with low-to moderate-load resistance training demonstrated the best effect in improving HbA1c, weight loss and cardiovascular risk factors; low-to moderate-load resistance training was more conducive to improving FBG. For 2hPG and blood pressure control, aerobic exercise was superior to other forms of exercise. Subgroup analysis demonstrated HbA1c, TC and BMI improved with increasing exercise duration. However, the optimal intensity and type of exercise remained moderate-intensity aerobic exercise combined with low-to moderate-intensity resistance training.

4.2 Comparisons with previous studies

The main pathological feature of prediabetes is impaired blood glucose regulation; both IFG and IGT have insulin resistance and abnormal insulin secretion (43, 44). IFG results from hepatic insulin resistance and impaired islet β -cell function, mainly manifested by impaired fasting blood glucose levels (44, 45). Conversely, IGT is caused by peripheral insulin resistance, notably in skeletal muscle, and is mainly characterized by impaired glucose tolerance and elevated blood glucose levels two hours after meals (44). Since IFG and IGT show distinct characteristics in pathophysiological mechanisms and clinical outcomes, therapies attempting to normalize hyperglycemia may differentially impact each phenotype.

The results of this review identified low-to moderate-load resistance training as the best intervention to improve FBG. Several clinical studies have demonstrated that resistance training reduces FBG levels in patients with diabetes as well as those with prediabetes (15, 33, 35). This is because resistance training can increase the activation of glycogen synthase (GS) through the inhibition of glycogen synthase kinase 3β (GSK3β) by AKT, which can lead to the eventual synthesis of glycogen (46–48). Second, the researchers observed that resistance training increases protein synthesis in muscle, either by activating the IGF-1/PI3K/AKT pathway or by reducing adenosine monophosphate-activated protein kinase (AMPK)-mediated mTOR inhibition (49). Increasing muscle mass can reduce muscle resistance to insulin to lower FBG levels. Finally, transiently activated AMPK may lead to the translocation of glucose transporter (GLUT-4) in skeletal muscle (49, 50), enhance fatty acid oxidation to increase glucose uptake, and ultimately improve insulin sensitivity, and lower FBG while increasing lipid clearance in the blood (47). However, there is also conflicting evidence. In Eikenberg et al's study (51), patients with prediabetes were classified into subtypes for resistance training, and the results showed no improvement in FBG in patients with IFG. In terms of intensity, Tsai et al. (52) performed resistance training at different intensities in non-obese elderly patients with prediabetes and found that short-term high-intensity resistance training was more effective in normalizing glucose levels. It has been shown that high-intensity resistance training can increase muscle stimulation of glucose uptake and glycogen synthesis, and that an increase in GLUT-4 content may result from the greater degree of muscle fiber recruitment, leading to a consistent improvement in metabolic control and insulin sensitivity (53). However, some scholars have concluded that there is no correlation between elevated muscle mass or physical function and advancement in glycemic regulation. It is believed that this is due to the fact that better glycemic control does not rely on modifications in muscle size, but rather on changes occurring within the muscle (54). There is currently no consensus in the scientific literature regarding the aforementioned topic, which remains an area for future research. Because of the limited sample sizes of the studies that have been done, there is a lack of research on the effects of different types and intensities of exercise on different subgroups of patients with prediabetes. In addition, a number of uncontrollable factors, such as dietary habits, the timing of meals, frequency of exercise, and the design of the resistance training program, can significantly influence the results of the studies. For instance, one study found that patients with continuous glucose monitoring (CGM) decreased blood glucose levels during resistance training up to 24 hours after resistance training, but the effect may depend on meal time (55). Meanwhile, one study found that for the same intensity of resistance training, multijoint exercise recruited more adjacent muscle groups than monojoint exercise. This allows more muscle mass and fibers to be involved in the movement during multi-joint exercise, which may lead to a greater reduction in FBG (56, 57). In conclusion, further research needs to

determine appropriate resistance training prescriptions for patients with different subtypes of prediabetes, particularly regarding intensity, the relationship between resistance training and meal timing, and exercise design.

For aerobic exercise, our results suggested that vigorous-intensity aerobic exercise is more effective in improving 2-hour postprandial glucose and systolic blood pressure, whereas moderate-intensity aerobic exercise improves diastolic blood pressure. To summarize, aerobic training can enhance both blood pressure control ability and insulin secretion two hours after consuming a meal. Several meta-analyses and RCTs have also confirmed that vigorous-intensity aerobic exercise significantly improves 2hPG levels, particularly in patients with IGT (35, 58, 59). Aerobic exercise increases peak oxygen consumption and can improve glucose tolerance, whole-body insulin sensitivity, and cardiovascular adaptation (32). In contrast to resistance training, aerobic exercise has no significant effect on muscle strength. Furthermore, aerobic exercise effectively induces GLUT4 enhancement factor, increasing GLUT4 expression and improved glycemic control (60, 61). Elevated 2hPG levels are typically attributed to diminished early insulin secretion, making enhancing islet β -cell function imperative for clinical significance. One study found that altered islet β -cell function was unrelated to VO_2max (32). However, the STRRIDE study (62) showed that moderate and vigorous exercise improves β -cell function through different mechanisms in sedentary, overweight sedentary overweight adults. Vigorous intensity exercise was associated with an improvement in insulin sensitivity and a compensatory decrease in insulin secretion, whereas low and moderate intensity exercise was only associated with an improvement in insulin sensitivity. A meta-analysis demonstrated that aerobic exercise of moderate to high intensity for more than 150 minutes per week for at least 6 weeks was associated with lower SBP and DBP in patients with type 2 diabetes (63). This has been attributed to regular aerobic exercise increasing nitric oxide synthesis and action and improving endothelium-dependent vasodilation (64). However, aerobic exercise can be categorized into moderate continuous training (MCT) and high intensity interval training (HIIT). Both are associated with improvements in arterial structure and function (56, 65, 66). A recent review highlighted the potential of HIIT to improve glycemic control to a greater extent than MCT (67). Physiological studies have shown that continuous exercise can produce more reactive oxygen species, leading to increased oxidative stress, which may compromise nitric oxide bioavailability and attenuate the beneficial effects of exercise on the endothelium (68, 69). HIIT may limit these effects on nitric oxide bioavailability, as the exercise session is always followed by a recovery period (67, 70). It is also a reference point for the development of exercise prescriptions for our patients with prediabetes. In this study, the age of the population included was generally over 55 years. Therefore, we still consider moderate-intensity aerobic exercise to be the preferred type of exercise to reduce 2-hour postprandial blood glucose, and we can include short rest periods during exercise.

The efficacy of the combined aerobic and resistance training approach has been the subject of numerous studies (15, 28, 35, 71–73). This study differentiated intensity and showed that a combination of moderate-intensity aerobic exercise and low-to moderate-intensity resistance training can improve HbA1c, reduce weight, and reduce cardiovascular risk. The combination of aerobic and resistance training has been recommended by renowned institutions, including the American College of Sports Medicine, Belgian Physical Therapy Association, European Society of Cardiology and Exercise and Sports Science Australia (74–77). The results of our analyses were not only consistent with guideline-recommended interventions, but also confirmed that moderate-intensity combined exercise was the most effective modality. One study discovered that combined aerobic and resistance training had an additional effect without interference from simultaneous training (78). Combined exercise uses three methods to maximize glycemic control and improve body weight and cardiovascular outcomes. Firstly, exercise activates the insulin signaling pathway associated with AKT/PKB, increasing insulin receptor content and phosphorylation levels (61). Secondly, it can enhance the pathophysiological pathways associated with insulin resistance, upregulating the expression of GLUT 4 glucose transporters, increasing their translocation, promoting cellular glucose utilization and improving insulin resistance (61, 79, 80). These pathways comprise promoting mitochondrial biosynthesis and attenuating insulin resistance through activation of the AMPK/PGC-1α (Proliferator-activated receptor ɤ coactivator-α) pathway (81); inhibiting nuclear factor-κB (NF-κB) expression, reducing the levels of inflammatory factors such as tumor necrosis factor-alpha (TNF-α), exerting its anti-inflammatory effect (81, 82); stimulating the antioxidant mediator, nuclear erythroid 2 p45-related factor 2 (Nrf2), thereby enhancing the expression of glutathione to counteract oxidative stress caused by diabetes (83, 84); increasing the levels of galanin peptide and gene expression significantly to accelerate GLUT4 translocation and glucose uptake in myocytes and adipocytes (85). Finally, physical activity contracts skeletal muscle, enhances Ca^{2+} influx, increases osteocalcin, and boosts capillary flow to raise GLUT 4 translocation in the cell membrane, thereby promoting glucose uptake by muscle cells (72). During this process, regulation of adiponectin, visfatin, omentin-1 and leptin increases fatty acid release from adipocytes and fatty acid oxidation capacity, thereby increasing insulin sensitivity, minimizing lipid deposition in blood vessels, reducing visceral fat weight and reducing the risk of cardiovascular disease (86, 87). High-intensity resistance training combined with aerobic exercise may be difficult for elderly or obese patients with prediabetes to stick to, and they may also be less safe when exercising. Therefore, moderate-intensity aerobic exercise combined with low-to moderate-intensity resistance exercise is recommended.

4.3 Strengths and limitations

This study had several advantages and disadvantages. First, the review was systematic and exhaustive, with a considerable patients with prediabetes sample size (n=1946) being included, providing the ability to detect statistically significant mean differences. Second, only randomized controlled trials (RCT) were included, which is the gold standard for assessing the effectiveness of the intervention. Thirdly, the inclusion of general body morphology in the NMA outcome measures

also optimized this study, as this has generally been ignored in meta-studies evaluating exercise interventions for prediabetes. However, it is essential as a predictor and associated factor in all-cause mortality.

Our review shared some limitations with the studies that it has incorporated. Although we sought to limit heterogeneity by using stringent inclusion and exclusion criteria, the study population varied in several ways (age, recruited countries, and the proportion of male and female participants). Although nearly all of the included studies were conducted nearly 3 times per week, with a 50-minute exercise intervention, the duration of the intervention varied greatly. However, when included in the analysis as covariates, the intervention duration (number of weeks) could not explain the differences in the effect size of all outcomes in the NMA. In addition, the patients in the trials we included were not followed up, so the duration of the exercise effect could not be determined. We plan to extend this investigation in future trials.

Furthermore, most included trials reported risk factor outcome measures associated with inflammation as baseline data (TC, SBP, DBP, HDL, and LDL). However, they did not report these data in their post-intervention results. Exercise is considered as a cornerstone of preventing and managing metabolic syndrome, so future studies need to design these metabolic markers as primary outcomes rather than secondary or tertiary outcomes. This NMA identified some missing evidence associated with the exercise category. Aerobic exercise remains the most commonly used intervention, with resistance training and combined training representing only 14.85% and 3.75%, respectively. Often, due to limited data on direct comparison of specific interventions, especially for resistance training versus joint training, readers should interpret these results with caution as the lack of direct evidence, which makes the analysis less reliable, suggesting the need for further studies of resistance training and joint exercise in patients with prediabetes, 16 of 24 RCT trials at moderate risk of ROB. Since participants and supervisors could not blind exercise training, the associated bias for experimenters and patients was high, and 11 studies still showed unclear randomized sequence generation bias for the gold standard of randomized controlled trials.

Overall, the quality of the studies we included in the NMA was moderate. Thus, the current NMA results should be interpreted in a conservative manner.

4.4 Implications and future research

The findings in our review provided strong evidence that moderate-intensity combination training is essential in improving glycemic regulation function and preventing conversion to type 2 diabetes of diabetes in patients with prediabetes, which provides new ideas for glycemic control. Furthermore, we advocate further researches to address several important issues. First, our results should be confirmed in different types of patients with prediabetes. In addition, future clinical studies should consider different types of precursor diabetes mellitus (impaired fasting blood glucose and impaired glucose tolerance) to explore and improve different exercise intervention prescriptions, and to provide theoretical support for a clinical exercise intervention in prediabetes.

5 Conclusions

Despite its limitations, our systematic review and meta-analysis have showcased the positive effects of moderate-intensity aerobic exercise, low-to moderate-load resistance training, and the combination of both on prediabetes. These findings can provide valuable guidance to clinicians when prescribing exercise to patients with prediabetes, and to patients when self-administering the intervention.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/Supplementary Material.

Author contributions

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2024.1308959/full#supplementary-material

References

1. Allegrante JP, Wells MT, Peterson JC. Interventions to support behavioral self-management of chronic diseases. *Annu Rev Public Health* (2019) 40:127–46. doi: 10.1146/annurev-publhealth-040218-044008

2. Rett K, Gottwald-Hostalek U. Understanding prediabetes: definition, prevalence, burden and treatment options for an emerging disease. *Curr Med Res Opin* (2019) 35 (9):1529–34. doi: 10.1080/03007995.2019.1601455

3. Carris NW, Magness RR, Labovitz AJ. Prevention of diabetes mellitus in patients with prediabetes. *Am J Cardiol* (2019) 123(3):507–12. doi: 10.1016/j.amjcard.2018.10.032

4. Duan D, Kengne AP, Echouffo-Tcheugui JB. Screening for diabetes and prediabetes. *Endocrinol Metab Clin North Am* (2021) 50(3):369–85. doi: 10.1016/j.ecl.2021.05.002

5. Huang D, Refaat M, Mohammedi K, Jayyousi A, Al Suwaidi J, Abi Khalil C. Macrovascular complications in patients with diabetes and prediabetes. *BioMed Res Int* (2017) 2017:7839101. doi: 10.1155/2017/7839101

6. Magkos F, Hjorth MF, Astrup A. Diet and exercise in the prevention and treatment of type 2 diabetes mellitus. *Nat Rev Endocrinol* (2020) 16(10):545–55. doi: 10.1038/s41574-020-0381-5

7. Mahat RK, Singh N, Arora M, Rathore V. Health risks and interventions in prediabetes: A review. *Diabetes Metab Syndr* (2019) 13(4):2803–11. doi: 10.1016/j.dsx.2019.07.041

8. Crandall JP, Knowler WC, Kahn SE, Marrero D, Florez JC, Bray GA, et al. The prevention of type 2 diabetes. *Nat Clin Pract Endocrinol Metab* (2008) 4(7):382–93. doi: 10.1038/ncpendmet0843

9. Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, et al. The prisma extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med* (2015) 162(11):777–84. doi: 10.7326/m14-2385

10. Higgins JPT, Green S, Cochrane Collaboration. *Cochrane handbook for systematic reviews for interventions*. (2011). Chichester: England.

11. Hedges LV. *The handbook of research synthesis*. New York (Ny: Russell Sage Foundation (1994).

12. Warren B, Pankow JS, Matsushita K, Punjabi NM, Daya NR, Grams M, et al. Comparative prognostic performance of definitions of prediabetes: A prospective cohort analysis of the atherosclerosis risk in communities (Aric) study. *Lancet Diabetes Endocrinol* (2017) 5(1):34–42. doi: 10.1016/s2213-8587(16)30321-7

13. Shamizadeh T, Jahangiry L, Sarbakhsh P, Ponnet K. Social cognitive theory-based intervention to promote physical activity among prediabetic rural people: A cluster randomized controlled trial. *Trials* (2019) 20(1):98. doi: 10.1186/s13063-019-3220-z

14. Yan J, Dai X, Feng J, Yuan X, Li J, Yang L, et al. Effect of 12-month resistance training on changes in abdominal adipose tissue and metabolic variables in patients with prediabetes: A randomized controlled trial. *J Diabetes Res* (2019) 2019:8469739. doi: 10.1155/2019/8469739

15. Dai X, Zhai L, Chen Q, Miller JD, Lu L, Hsue C, et al. Two-year-supervised resistance training prevented diabetes incidence in people with prediabetes: A randomised control trial. *Diabetes Metab Res Rev* (2019) 35(5):e3143. doi: 10.1002/dmrr.3143

16. Kramer MK, Vanderwood KK, Arena VC, Miller RG, Meehan R, Eaglehouse YL, et al. Evaluation of a diabetes prevention program lifestyle intervention in older adults: A randomized controlled study in three senior/community centers of varying socioeconomic status. *Diabetes Educ* (2018) 44(2):118–29. doi: 10.1177/0145721718759982

17. Slentz CA, Bateman LA, Willis LH, Granville EO, Piner LW, Samsa GP, et al. Effects of exercise training alone vs a combined exercise and nutritional lifestyle intervention on glucose homeostasis in prediabetic individuals: A randomised controlled trial. *Diabetologia* (2016) 59(10):2088–98. doi: 10.1007/s00125-016-4051-z

18. Gidlund E-K, von Walden F, Venojärvi M, Risérus U, Heinonen OJ, Norrbom J, et al. Humanin skeletal muscle protein levels increase after resistance training in men with impaired glucose metabolism. *Physiol Rep* (2016) 4(23):e13063.doi: 10.14814/phy2.13063

19. Liao H-C, Zhong S-G, Li P, Chen W-B, Cheng C, Wang Y-G, et al. Effects and mechanism of moderate aerobic exercise on impaired fasting glucose improvement. *Lipids Health Dis* (2015) 14:157. doi: 10.1186/s12944-015-0117-z

20. Herzig KH, Ahola R, Leppäluoto J, Jokelainen J, Jämsä T, Keinänen-Kiukaanniemi S. Light physical activity determined by a motion sensor decreases insulin resistance, improves lipid homeostasis and reduces visceral fat in high-risk subjects: prediabex study rct. *Int J Obes (Lond)* (2014) 38(8):1089–96. doi: 10.1038/ijo.2013.224

21. Venojärvi M, Wasenius N, Manderoos S, Heinonen OJ, Hernelahti M, Lindholm H, et al. Nordic walking decreased circulating chemerin and leptin concentrations in middle-aged men with impaired glucose regulation. *Ann Med* (2013) 45(2):162–70. doi: 10.3109/07853890.2012.727020

22. Fritz T, Caidahl K, Krook A, Lundström P, Mashili F, Osler M, et al. Effects of nordic walking on cardiovascular risk factors in overweight individuals with type 2 diabetes, impaired or normal glucose tolerance. *Diabetes Metab Res Rev* (2013) 29 (1):25–32. doi: 10.1002/dmrr.2321

23. Hansen E, Landstad BJ, Gundersen KT, Torjesen PA, Svebak S. Insulin sensitivity after maximal and endurance resistance training. *J Strength Cond Res* (2012) 26(2):327–34. doi: 10.1519/JSC.0b013e318220e70f

24. Alvarez C, Ramírez R, Flores M, Zúñiga C, Celis-Morales CA. [Effect of sprint interval training and resistance exercise on metabolic markers in overweight women]. *Rev Med Chil* (2012) 140(10):1289–96. doi: 10.4067/S0034-98872012001000008

25. Burtscher M, Gatterer H, Kunczicky H, Brandstätter E, Ulmer H. Supervised exercise in patients with impaired fasting glucose: impact on exercise capacity. *Clin J Sport Med* (2009) 19(5):394–8. doi: 10.1097/JSM.0b013e3181b8b6dc

26. Desch S, Sonnabend M, Niebauer J, Sixt S, Sareban M, Eitel I, et al. Effects of physical exercise versus rosiglitazone on endothelial function in coronary artery disease patients with prediabetes. *Diabetes Obes Metab* (2010) 12(9):825–8. doi: 10.1111/j.1463-1326.2010.01234.x

27. Eriksson J, Tuominen J, Valle T, Sundberg S, Sovijärvi A, Lindholm H, et al. Aerobic endurance exercise or circuit-type resistance training for individuals with impaired glucose tolerance? *Horm Metab Res* (1998) 30(1):37–41. doi: 10.1055/s-2007-978828

28. Malin SK, Gerber R, Chipkin SR, Braun B. Independent and combined effects of exercise training and metformin on insulin sensitivity in individuals with prediabetes. *Diabetes Care* (2012) 35(1):131–6. doi: 10.2337/dc11-0925

29. Marcell TJ, McAuley KA, Traustadóttir T, Reaven PD. Exercise training is not associated with improved levels of C-reactive protein or adiponectin. *Metabolism* (2005) 54(4):533–41. doi: 10.1016/j.metabol.2004.11.008

30. Marcus RL, Lastayo PC, Dibble LE, Hill L, McClain DA. Increased strength and physical performance with eccentric training in women with impaired glucose tolerance: A pilot study. *J Womens Health (Larchmt)* (2009) 18(2):253–60. doi: 10.1089/jwh.2007.0669

31. Roumen C, Corpeleijn E, Feskens EJM, Mensink M, Saris WHM, Blaak EE. Impact of 3-year lifestyle intervention on postprandial glucose metabolism: the slim study. *Diabetes Med* (2008) 25(5):597–605. doi: 10.1111/j.1464-5491.2008.02417.x

32. Rowan CP, Riddell MC, Gledhill N, Jamnik VK. Aerobic exercise training modalities and prediabetes risk reduction. *Med Sci Sports Exerc* (2017) 49(3):403–12. doi: 10.1249/MSS.0000000000001135

33. Yuan X, Dai X, Liu L, Hsue C, Miller JD, Fang Z, et al. Comparing the effects of 6 months aerobic exercise and resistance training on metabolic control and β-cell function in chinese patients with prediabetes: A multicenter randomized controlled trial. *J Diabetes* (2020) 12(1):25–37. doi: 10.1111/1753-0407.12955

34. Cheng S, Ge J, Zhao C, Le S, Yang Y, Ke D, et al. Effect of aerobic exercise and diet on liver fat in pre-diabetic patients with non-alcoholic-fatty-liver-disease: A randomized controlled trial. *Sci Rep* (2017) 7(1):15952. doi: 10.1038/s41598-017-16159-x

35. Liu L, Ma X, Xu H, Ruan S, Yuan X. Comparing the effects of 12 months aerobic exercise and resistance training on glucose metabolism among prediabetes phenotype: A explorative randomized controlled trial. *Prim Care Diabetes* (2021) 15(2):340–6. doi: 10.1016/j.pcd.2020.11.003

36. Gilbertson NM, Mandelson JA, Hilovsky K, Akers JD, Hargens TA, Wenos DL, et al. Combining supervised run interval training or moderate-intensity continuous training with the diabetes prevention program on clinical outcomes. *Eur J Appl Physiol* (2019) 119(7):1503–12. doi: 10.1007/s00421-019-04137-2

37. Sterne JAC, Savovi J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: A revised tool for assessing risk of bias in randomised trials [J]. *BMJ Clin Res*. (2019). 366: l4898.doi: 10.1136/bmj.l4898

38. O'Donoghue G, Blake C, Cunningham C, Lennon O, Perrotta C. What exercise prescription is optimal to improve body composition and cardiorespiratory fitness in adults living with obesity? A network meta-analysis. *Obes Rev* (2021) 22(2):e13137. doi: 10.1111/obr.13137

39. Shim SR, Kim SJ, Lee J, Rücker G. Network meta-analysis: application and practice using R software. *Epidemiol Health* (2019) 41:e2019013. doi: 10.4178/epih.e2019013

40. Rücker G. Network meta-analysis, electrical networks and graph theory. *Res Synth Methods* (2012) 3(4):312–24. doi: 10.1002/jrsm.1058

41. Higgins JP, Jackson D, Barrett JK, Lu G, Ades AE, White IR. Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies. *Res Synth Methods* (2012) 3(2):98–110. doi: 10.1002/jrsm.1044

42. Dias S, Welton NJ, Caldwell DM, Ades AE. Checking consistency in mixed treatment comparison meta-analysis. *Stat Med* (2010) 29(7-8):932–44. doi: 10.1002/sim.3767

43. Fonseca VA. Defining and characterizing the progression of type 2 diabetes. *Diabetes Care* (2009) 32 Suppl 2(Suppl 2):S151–6. doi: 10.2337/dc09-S301

44. Gaitan JM, Weltman A, Malin SK. Enhancing exercise responsiveness across prediabetes phenotypes by targeting insulin sensitivity with nutrition. *J Diabetes Res* (2017) 2017:8314852. doi: 10.1155/2017/8314852

45. Meyer C, Pimenta W, Woerle HJ, Van Haeften T, Szoke E, Mitrakou A, et al. Different mechanisms for impaired fasting glucose and impaired postprandial glucose tolerance in humans. *Diabetes Care* (2006) 29(8):1909–14. doi: 10.2337/dc06-0438

46. Case N, Thomas J, Sen B, Styner M, Xie Z, Galior K, et al. Mechanical regulation of glycogen synthase kinase 3β (Gsk3β) in mesenchymal stem cells is dependent on akt protein serine 473 phosphorylation via mtorc2 protein. *J Biol Chem* (2011) 286 (45):39450–6. doi: 10.1074/jbc.M111.265330

47. Strasser B, Pesta D. Resistance training for diabetes prevention and therapy: experimental findings and molecular mechanisms. *BioMed Res Int* (2013) 2013:805217. doi: 10.1155/2013/805217

48. Christ-Roberts CY, Pratipanawatr T, Pratipanawatr W, Berria R, Belfort R, Kashyap S, et al. Exercise training increases glycogen synthase activity and glut4 expression but not insulin signaling in overweight nondiabetic and type 2 diabetic subjects. *Metabolism* (2004) 53(9):1233–42. doi: 10.1016/j.metabol.2004.03.022

49. Dreyer HC, Fujita S, Cadenas JG, Chinkes DL, Volpi E, Rasmussen BB. Resistance exercise increases ampk activity and reduces 4e-bp1 phosphorylation and protein synthesis in human skeletal muscle. *J Physiol* (2006) 576(Pt 2):613–24. doi: 10.1113/jphysiol.2006.113175

50. Mu J, Brozinick JT Jr., Valladares O, Bucan M, Birnbaum MJ. A role for amp-activated protein kinase in contraction- and hypoxia-regulated glucose transport in skeletal muscle. *Mol Cell* (2001) 7(5):1085–94. doi: 10.1016/s1097-2765(01)00251-9

51. Eikenberg JD, Savla J, Marinik EL, Davy KP, Pownall J, Baugh ME, et al. Prediabetes phenotype influences improvements in glucose homeostasis with resistance training. *PloS One* (2016) 11(2):e0148009. doi: 10.1371/journal.pone.0148009

52. Tsai SH, Cheng HC, Liu HW. Effects of volume-matched resistance training with different loads on glycemic control, inflammation, and body composition in prediabetic older adults. *Appl Physiol Nutr Metab* (2021) 46(11):1400–6. doi: 10.1139/apnm-2021-0355

53. Roberts CK, Little JP, Thyfault JP. Modification of insulin sensitivity and glycemic control by activity and exercise. *Med Sci Sports Exerc* (2013) 45(10):1868–77. doi: 10.1249/MSS.0b013e318295cdbb

54. Geirsdottir OG, Arnarson A, Briem K, Ramel A, Jonsson PV, Thorsdottir I. Effect of 12-week resistance exercise program on body composition, muscle strength, physical function, and glucose metabolism in healthy, insulin-resistant, and diabetic elderly Icelanders. *J Gerontol A Biol Sci Med Sci* (2012) 67(11):1259–65. doi: 10.1093/gerona/gls096

55. Heden TD, Liu Y, Kanaley JA. A comparison of adipose tissue interstitial glucose and venous blood glucose during postprandial resistance exercise in patients with type 2 diabetes. *J Appl Physiol (1985)* (2018) 124(4):1054–61. doi: 10.1152/japplphysiol.00475.2017

56. Olver TD, Laughlin MH. Endurance, interval sprint, and resistance exercise training: impact on microvascular dysfunction in type 2 diabetes. *Am J Physiol Heart Circ Physiol* (2016) 310(3):H337–50. doi: 10.1152/ajpheart.00440.2015

57. Gentil P, Fisher J, Steele J. A review of the acute effects and long-term adaptations of single- and multi-joint exercises during resistance training. *Sports Med* (2017) 47(5):843–55. doi: 10.1007/s40279-016-0627-5

58. Wang Y, Li H, Yang D, Wang M, Han Y, Wang H. Effects of aerobic exercises in prediabetes patients: A systematic review and meta-analysis. *Front Endocrinol (Lausanne)* (2023) 14:1227489. doi: 10.3389/fendo.2023.1227489

59. Malin SK, Kirwan JP. Fasting hyperglycaemia blunts the reversal of impaired glucose tolerance after exercise training in obese older adults. *Diabetes Obes Metab* (2012) 14(9):835–41. doi: 10.1111/j.1463-1326.2012.01608.x

60. McGee SL, Hargreaves M. Exercise and skeletal muscle glucose transporter 4 expression: molecular mechanisms. *Clin Exp Pharmacol Physiol* (2006) 33(4):395–9. doi: 10.1111/j.1440-1681.2006.04362.x

61. Imierska M, Kurianiuk A, Błachnio-Zabielska A. The influence of physical activity on the bioactive lipids metabolism in obesity-induced muscle insulin resistance. *Biomolecules* (2020) 10(12). doi: 10.3390/biom10121665

62. AbouAssi H, Slentz CA, Mikus CR, Tanner CJ, Bateman LA, Willis LH, et al. The effects of aerobic, resistance, and combination training on insulin sensitivity and secretion in overweight adults from strride at/rt: A randomized trial. *J Appl Physiol (1985)* (2015) 118(12):1474–82. doi: 10.1152/japplphysiol.00509.2014

63. Figueira FR, Umpierre D, Cureau FV, Zucatti AT, Dalzochio MB, Leitão CB, et al. Association between physical activity advice only or structured exercise training with blood pressure levels in patients with type 2 diabetes: A systematic review and meta-analysis. *Sports Med* (2014) 44(11):1557–72. doi: 10.1007/s40279-014-0226-2

64. Park S, Kim J, Lee J. Effects of exercise intervention on adults with both hypertension and type 2 diabetes mellitus: A systematic review and meta-analysis. *J Cardiovasc Nurs* (2021) 36(1):23–33. doi: 10.1097/jcn.0000000000000651

65. Francois ME, Pistawka KJ, Halperin FA, Little JP. Cardiovascular benefits of combined interval training and post-exercise nutrition in type 2 diabetes. *J Diabetes Complications* (2018) 32(2):226–33. doi: 10.1016/j.jdiacomp.2017.10.002

66. Davies MJ, D'Alessio DA, Fradkin J, Kernan WN, Mathieu C, Mingrone G, et al. Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the american diabetes association (Ada) and the european association for the study of diabetes (Easd). *Diabetologia* (2018) 61(12):2461–98. doi: 10.1007/s00125-018-4729-5

67. Magalhães JP, Melo X, Correia IR, Ribeiro RT, Raposo J, Dores H, et al. Effects of combined training with different intensities on vascular health in patients with type 2 diabetes: A 1-year randomizedcontrolledtrial. *CardiovascDiabetol* (2019) 18(1):34. doi:10.1186/s12933-019-0840-2

68. Green DJ, Hopman MT, Padilla J, Laughlin MH, Thijssen DH. Vascular adaptation to exercise in humans: role of hemodynamic stimuli. *Physiol Rev* (2017) 97(2):495–528. doi: 10.1152/physrev.00014.2016

69. Bergholm R, Mäkimattila S, Valkonen M, Liu ML, Lahdenperä S, Taskinen MR, et al. Intense physical training decreases circulating antioxidants and endothelium-dependent vasodilatation *in vivo*. *Atherosclerosis* (1999) 145(2):341–9. doi:10.1016/s0021-9150(99)00089-1

70. Ramos JS, Dalleck LC, Tjonna AE, Beetham KS, Coombes JS. The impact of high-intensity interval training versus moderate-intensity continuous training on vascular function: A systematic review and meta-analysis. *Sports Med* (2015) 45 (5):679–92. doi: 10.1007/s40279-015-0321-z

71. Halliday TM, Savla J, Marinik EL, Hedrick VE, Winett RA, Davy BM. Resistance training is associated with spontaneous changes in aerobic physical activity but not overall diet quality in adults with prediabetes. *Physiol Behav* (2017) 177:49–56. doi: 10.1016/j.physbeh.2017.04.013

72. Chen X, Zhao S, Hsue C, Dai X, Liu L, Miller JD, et al. Effects of aerobic training and resistance training in reducing cardiovascular disease risk for patients with prediabetes: A multi-center randomized controlled trial. *Prim Care Diabetes* (2021) 15(6):1063–70. doi: 10.1016/j.pcd.2021.08.013

73. Luo X, Wang Z, Li B, Zhang X, Li X. Effect of resistance vs. Aerobic exercise in pre-diabetes: an rct. *Trials* (2023) 24(1):110. doi: 10.1186/s13063-023-07116-3

74. Rydén L, Grant PJ, Anker SD, Berne C, Cosentino F, Danchin N, et al. Esc guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the easd: the task force on diabetes, pre-diabetes, and cardiovascular diseases of the european society of cardiology (Esc) and developed in collaboration with the european association for the study of diabetes (Easd). *Eur Heart J* (2013) 34(39):3035–87. doi: 10.1093/eurheartj/eht108

75. Colberg SR, Albright AL, Blissmer BJ, Braun B, Chasan-Taber L, Fernhall B, et al. Exercise and type 2 diabetes: american college of sports medicine and the american diabetes association: joint position statement. Exercise and type 2 diabetes. *Med Sci Sports Exerc* (2010) 42(12):2282–303. doi: 10.1249/MSS.0b013e3181eeb61c

76. Hansen D, Peeters S, Zwaenepoel B, Verleyen D, Wittebrood C, Timmerman N, et al. Exercise assessment and prescription in patients with type 2 diabetes in the private and home care setting: clinical recommendations from axxon (Belgian physical therapy association). *Phys Ther* (2013) 93(5):597–610. doi: 10.2522/ptj.20120400

77. Hordern MD, Dunstan DW, Prins JB, Baker MK, Singh MA, Coombes JS. Exercise prescription for patients with type 2 diabetes and pre-diabetes: A position statement from exercise and sport science Australia. *J Sci Med Sport* (2012) 15(1):25–31. doi: 10.1016/j.jsams.2011.04.005

78. Villareal DT, Aguirre L, Gurney AB, Waters DL, Sinacore DR, Colombo E, et al. Aerobic or resistance exercise, or both, in dieting obese older adults. *N Engl J Med* (2017) 376(20):1943–55. doi: 10.1056/NEJMoa1616338

79. Zanuso S, Sacchetti M, Sundberg CJ, Orlando G, Benvenuti P, Balducci S. Exercise in type 2 diabetes: genetic, metabolic and neuromuscular adaptations. A review of the evidence. *Br J Sports Med* (2017) 51(21):1533–8. doi: 10.1136/bjsports-2016-096724

80. Di Murro E, Di Giuseppe G, Soldovieri L, Moffa S, Improta I, Capece U, et al. Physical activity and type 2 diabetes: in search of a personalized approach to improving β-cell function. *Nutrients* (2023) 15(19). doi: 10.3390/nu15194202

81. Tian J, Fan J, Zhang T. Mitochondria as a target for exercise-mitigated type 2 diabetes. *J Mol Histol* (2023) 54(6):543–57. doi: 10.1007/s10735-023-10158-1

82. Ferrari F, Bock PM, Motta MT, Helal L. Biochemical and molecular mechanisms of glucose uptake stimulated by physical exercise in insulin resistance state: role of inflammation. *Arq Bras Cardiol* (2019) 113(6):1139–48. doi: 10.5935/abc.20190224

83. Lew JK, Pearson JT, Schwenke DO, Katare R. Exercise mediated protection of diabetic heart through modulation of microrna mediated molecular pathways. *Cardiovasc Diabetol* (2017) 16(1):10. doi: 10.1186/s12933-016-0484-4

84. Grotle AK, Stone AJ. Exaggerated exercise pressor reflex in type 2 diabetes: potential role of oxidative stress. *Auton Neurosci* (2019) 222:102591. doi: 10.1016/j.autneu.2019.102591

85. Fang P, He B, Shi M, Zhu Y, Bo P, Zhang Z. Crosstalk between exercise and galanin system alleviates insulin resistance. *Neurosci Biobehav Rev* (2015) 59:141–6. doi: 10.1016/j.neubiorev.2015.09.012

86. Zouhal H, Zare-Kookandeh N, Haghighi MM, Daraei A, de Sousa M, Soltani M, et al. Physical activity and adipokine levels in individuals with type 2 diabetes: A literature review and practical applications. *Rev Endocr Metab Disord* (2021) 22 (4):987–1011. doi: 10.1007/s11154-021-09657-x

87. Sousa RAL, Improta-Caria AC, Souza BSF. Exercise-linked irisin: consequences on mental and cardiovascular health in type 2 diabetes. *Int J Mol Sci* (2021) 22(4). doi: 10.3390/ijms22042199

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Glossary

IGT	Impaired Fasting Glucose
IGT	Impaired Glucose Tolerance
CGI	Combined IFG/IGT
FBG	Asting Blood-Glucose
2hPG	2-Hour Post-Meal Blood Glucose
BW	Body Weight
TC	Total Cholesterol
DBP	Diastolic Blood Pressure
SBP	Systolic Blood Pressure
$VO2_{max}$	Maximal Oxygen Consumption
HR_{max}	Maximal Heart Rate
HRR	Heart Rate Reserve
1RM	One-Repetition Maximum
Met	Metabolic Equivalent of Energy
AT-V	Vigorous-Intensity Aerobic Exercise
AT-M	Moderate-Intensity Aerobic Exercise
RT-H	High Load Resistance Training
RT-L	Low To Moderate-Load Resistance Training
AT-V +RT-H	Combined Vigorous-Intensity Aerobic Exercise
AT-M +RT-L	Combined Moderate-Intensity Aerobic Exercise with Low-to Moderate-Load Resistance Training
CON	No Exercise
ADA	American Diabetes Association
WHO	World Health Organization
ACSM	American College of Sports Medicine
FRS	The Framingham Risk Score
CVD	Cardiovascular disease
GS	Glycogen synthase
GSK3β	Glycogen synthase kinase 3βAKT/PKB, Protein kinase BIGF-1, Insulin-like growth factor 1
AMPK	Adenosine monophosphate-activated protein kinase
GLUT-4	Glucose transporter
CGM	Continuous glucose monitoring
PGC-1α	Proliferator-activated receptorγcoactivator-α
NF-κB	Nuclear factor-κB
TNF- α	Tumor necrosis factor-alpha
Nrf2	Nuclear erythroid 2 p45-related factor 2

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Global trends in burden of type 2 diabetes attributable to physical inactivity across 204 countries and territories, 1990-2019

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Background: To promote a comprehensive understanding of global trends and burden of type 2 diabetes attributable to physical inactivity.

Methods: We utilized data regarding mortality, disability-adjusted life years (DALYs), as well as age-standardized mortality rates (ASMR) and DALYs rates (ASDR) derived from the global burden of disease study 2019 to evaluate the impact of physical inactivity on the prevalence of type 2 diabetes in 204 countries and territories over the period from 1990 to 2019. This method facilitated the analysis of the diabetes burden across different ages, genders, and regions. To determine the long-term progression of type 2 diabetes prevalence, we computed the estimated annual percentage change (EAPC) in burden rates.

Results: Globally, the number of deaths and DALYs from type 2 diabetes due to physical inactivity more than doubled between 1990 and 2019. Concurrently, there was an increase in the ASMR and ASDR, with EAPC of 0.26 (95% CI: 0.13-0.39) and 0.84 (95% CI: 0.78-0.89), respectively. As of 2019, the global ASMR and ASDR for physical inactivity stood at 1.6 (95% UI: 0.8-2.7) per 100 000 and 55.9 (95% UI: 27.2-97.6) per 100 000, respectively. Notable disparities were observed in the type 2 diabetes burden associated with physical inactivity worldwide, with higher sociodemographic index (SDI) countries experiencing lower ASDR and ASMR compared to lower SDI countries. Initially, females exhibited higher ASMR and ASDR than males, but this gender disparity in ASMR and ASDR has lessened in recent years. The mortality and DALYs rates associated with physical inactivity exhibit an inverted V-shaped pattern across various age groups, predominantly affecting the elderly population.

Conclusion: Between 1990 and 2019, there was a marked rise in the worldwide burden of type 2 diabetes associated with physical inactivity, underscoring the role of physical inactivity as a key changeable risk factor in the global landscape of this disease. This necessitates additional research to explore the variables contributing to the varying levels of disease burden across different countries and between sexes. Furthermore, it calls for the formulation of public health policies aimed at guiding prevention tactics, promoting early detection, and enhancing the management of type 2 diabetes.

KEYWORDS

global burden, type 2 diabetes, physical inactivity, mortality, disability-adjusted life years, sociodemographic index

Introduction

Over the past few decades, there has been a significant increase in diabetes cases, closely linked to changes in lifestyle habits (1). The International Diabetes Federation reports that in 2021, about 536.6 million adults aged 20-79 were living with diabetes, and this number is expected to surge to 783.2 million by 2045 (2). Diabetes poses a substantial challenge to public health, profoundly affecting individuals, families, and communities worldwide (3). Type 2 diabetes, which accounts for over 90% of all diabetes cases globally, is a metabolic condition marked by insufficient insulin production and resistance, leading to high blood sugar levels. The 2019 global burden of disease (GBD) study provides recent data, estimating that the worldwide prevalence, mortalities, and disability-adjusted life years (DALYs) due to type 2 diabetes were approximately 437.9 million, 1.5 million, and 66.3 million, respectively (4).

Four major non-communicable diseases (cardiovascular diseases, diabetes, cancer and chronic respiratory disease) cause just over 70% of all preventable deaths occurring worldwide, around 41 million people (5). Tobacco, physical inactivity, alcohol abuse, and unhealthy diets increase the risk of dying from non-communicable diseases (6). As of 2016, it was estimated that about 27.5% of the global population exhibited insufficient physical activity, with a 95% uncertainty interval (UI) of 25.0-32.2 (7). Recognized as a worldwide health crisis, physical inactivity significantly contributes to the overall burden of disease. In 2008, lack of physical activity was estimated to be responsible for approximately 9% of premature mortalities worldwide, equating to over 5.3 million out of the total 57 million deaths (8). Moreover, the economic impact of physical inactivity is substantial. In 2013, it led to a global loss of productivity amounting to $13.7 billion (9).

Despite physical inactivity being recognized as a key modifiable risk factor for type 2 diabetes (10, 11), global epidemiological investigations of this association remain limited, often concentrating on smaller developed country samples failing to reflect worldwide trends comprehensively. However, physical activity levels differ globally, potentially impacting regional type 2 diabetes burdens. Therefore, this study utilizes global epidemiological data to evaluate changes in type 2 diabetes burden attributable to physical inactivity across 204 countries/territories from 1990-2019, informing targeted diabetes prevention and control strategies globally.

Methods

Data source

This research utilized data from the GBD 2019. The GBD estimation methodology involves identifying multiple relevant data sources for each disease or injury, including censuses, surveys, civil registries, disease registries, health services, environmental monitors, imaging, notifications, and others. These are identified via systematic reviews of published studies, government/organizational websites, reports, and GBD collaborator datasets. Each newly identified and obtained source receives a unique identifier from the librarian team and inclusion into the Global Health Data Exchange (GHDx: https://ghdx.healthdata.org/). The GHDx publicly provides the metadata and available data for all sources used in GBD estimates, allowing to identify the specific sources used to estimate any disease/injury outcome (12, 13).

Our approach adhered to the methodological principles and analytic techniques specified in GBD 2019, which are elaborated in other publications (14). This initiative offered epidemiological insights and quantifications for 369 diseases and injuries in 204 countries and territories spanning from 1990 to 2019 (13). Utilizing comprehensive datasets across different ages, time periods, regions, and health categories, the GBD network employed uniform Bayesian methods to produce disease-specific estimates. This integration of diverse data sources with modeling techniques enabled the estimation of global disease burden across nations and regions despite gaps in population health information (12).

In the GBD 2019, risk factors are stratified into four tiers within a causality framework, ranging from the most general (Level 1, such as NCDs) to the most specific (Level 4, like type 2 diabetes), to gauge their impact on disease burden (15). For diagnosing type 2 diabetes, the primary benchmark is fasting plasma glucose levels above 126 mg/dl or ongoing treatment with medication or insulin for T2DM. Yet, in the GBD 2019, additional indicators such as oral glucose tolerance, and postprandial glucose tests were also recognized, albeit varying from the main diagnostic criteria (4). Consequently, these alternate diagnostic approaches, serving as data inputs, underwent adjustment before the start of the modeling phase. Physical inactivity, categorized as Level 2, was defined as less than 3,000-4,500 metabolic equivalent (MET) minutes per week, averaged across occupational, household, transport, and leisure activities. The MET minutes per week was calculated as follows: minutes of activity/day × days per week × MET level (16). Data on physical inactivity were compiled from 376 sources worldwide (17).

We sourced data on the impact of physical inactivity on type 2 diabetes globally from 1990 to 2019, by country, region, and gender, from the GHDx. These data encompassed 204 countries and territories, divided into five groups based on the sociodemographic index (SDI): high, high-middle, middle, low-middle, and low. SDI, a measure of regional development, is calculated from the total fertility rate among females under 25, education attainment for individuals aged 15 and older, and the lagged per capita gross domestic product, with values ranging from 0 (least developed) to 1 (most developed) (12). Furthermore, these countries were grouped into 21 geographical regions (Table 1). For detailed analysis, age was segmented into 15 categories, including fourteen 5-year intervals from 25-94 years and one category for ages ≥95 years.

Statistical analysis

To assess the global, regional, and national burden of type 2 diabetes due to physical inactivity, we utilized metrics including

deaths, age-standardized mortality rates (ASMR), DALYs, and age-standardized disability rates (ASDR). The estimated annual percentage change (EAPC) was employed to analyze the trends in age-standardized rates (ASR) from 1990 to 2019 (18). Trends in ASR were categorized as increasing, decreasing, or stable based on whether the EAPC and its 95% CI were greater than 0, less than 0, or included 0, respectively (19). These analyses were performed using the R software (version 4.0.3).

Results

Type 2 diabetes deaths and ASMR associated with physical inactivity

Globally, the number of type 2 diabetes deaths associated with physical inactivity markedly rose from 49.8 thousand (95% UI: 24.5-84.6) in 1990 to 125.2 thousand (95% UI: 62.1-208.3) in 2019

TABLE 1 The global type 2 diabetes burden attributable to physical inactivity in 1990 and 2019 and the temporal trends from 1990 to 2019.

characteristic	1990				2019				EAPC (1990-2019)	
	Death cases, n × 10^3 (95% UI)	ASMR per 10^5, n (95% UI)	DALYs, n × 10^3 (95% UI)	ASDR per 10^5, n (95% UI)	Death cases, n × 10^3 (95% UI)	ASMR per 10^5, n (95% UI)	DALYs, n × 10^3 (95% UI)	ASDR per 10^5, n (95% UI)	ASMR, n (95% CI)	ASDR, n (95% CI)
Global	49.8 (24.5-84.6)	1.5 (0.8-2.5)	1719.8 (782-3071.2)	45 (21.3-79.5)	125.2 (62.1-208.3)	1.6 (0.8-2.7)	4549.2 (2188.5-7969.5)	55.9 (27.2-97.6)	0.26 (0.13-0.39)	0.84 (0.78-0.89)
Sex										
Male	18.9 (8.5-33.8)	1.4 (0.6-2.4)	691.5 (288.5-1292.4)	40.5 (17.9-73.9)	54 (25.7-91.5)	1.6 (0.8-2.7)	2038.8 (898.4-3704.7)	54.3 (25-97.6)	0.51 (0.37-0.65)	0.99 (0.93-1.05)
Female	30.9 (16-50.9)	1.6 (0.8-2.6)	1028.3 (500.4-1788.9)	49.1 (24.1-84.6)	71.2 (37-115.6)	1.6 (0.8-2.6)	2510.4 (1251.7-4297.5)	57.5 (28.6-98.4)	0.09 (-0.04-0.23)	0.73 (0.66-0.79)
Socio-demographic index										
High SDI	12.7 (6.1-21.3)	1.2 (0.6-2)	420.3 (187.2-765.9)	40.5 (17.8-74.8)	19.6 (9.6-32.2)	0.9 (0.4-1.5)	879 (410.8-1574.4)	49.7 (23-91.8)	-1.48 (-1.81–1.15)	0.63 (0.54-0.73)
High-middle SDI	12.6 (6.5-20.3)	1.4 (0.7-2.2)	445.7 (213.5-759)	43 (21.1-72.5)	25.6 (13.4-40.5)	1.3 (0.7-2)	963.1 (481.4-1662.4)	47.6 (23.8-81.9)	-0.2 (-0.33–0.07)	0.39 (0.29-0.49)
Middle SDI	13.1 (6.1-22.9)	1.7 (0.8-2.8)	466.9 (208.9-839.4)	48.1 (22.4-84.4)	44.2 (21.6-74.5)	2.1 (1-3.5)	1545.7 (707.7-2717.5)	63.8 (30-110.3)	0.89 (0.82-0.96)	1.04 (0.99-1.09)
Low-middle SDI	8.2 (4.1-14.2)	1.9 (1-3.2)	280.2 (131.6-505)	51.3 (25.5-90.2)	27.4 (14-45.5)	2.5 (1.3-4.1)	872.1 (429.4-1524.2)	68.1 (34.2-115.4)	1.07 (0.91-1.24)	1.19 (1.09-1.29)
Low SDI	3.1 (1.4-5.9)	1.8 (0.9-3.2)	104.5 (44.7-200.8)	47.9 (21.8-88.1)	8.2 (3.9-14.3)	2.1 (1-3.6)	283.5 (125.3-520.1)	58.5 (27.3-105.9)	0.73 (0.56-0.89)	0.96 (0.84-1.09)
Region										
Andean Latin America	0.2 (0.1-0.3)	1 (0.4-1.8)	5.5 (2-11.2)	27.9 (10.2-55.8)	0.9 (0.4-1.6)	1.7 (0.7-3.1)	28.4 (11.3-54.8)	51.5 (20.7-98.6)	2.1 (1.93-2.26)	2.18 (2.1-2.26)
Australasia	0.3 (0.1-0.5)	1.3 (0.7-2.1)	8.5 (3.9-14.8)	36.7 (16.5-64.1)	0.7 (0.4-1.1)	1.3 (0.7-2)	25.6 (12.6-43.2)	52.8 (25.3-91.2)	-0.49 (-0.84–0.13)	1.08 (0.92-1.25)

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TABLE 1 Continued

characteristic	1990				2019				EAPC (1990-2019)	
	Death cases, n × 10^3 (95% UI)	ASMR per 10^5, n (95% UI)	DALYs, n × 10^3 (95% UI)	ASDR per 10^5, n (95% UI)	Death cases, n × 10^3 (95% UI)	ASMR per 10^5, n (95% UI)	DALYs, n × 10^3 (95% UI)	ASDR per 10^5, n (95% UI)	ASMR, n (95% CI)	ASDR, n (95% CI)
Region										
Caribbean	1.3 (0.7-2)	5.3 (2.9-8.3)	40.8 (19.7-69.1)	157.9 (77.2-265.7)	2.6 (1.4-4)	5 (2.7-7.8)	95.2 (48.1-160.7)	184.1 (93.5-310.6)	-0.3 (-0.37–0.22)	0.47 (0.41-0.53)
Central Asia	0.2 (0.1-0.3)	0.4 (0.2-0.7)	7.9 (3.3-15.7)	17.4 (7.6-33.6)	0.8 (0.3-1.4)	1.3 (0.6-2.3)	31.4 (13.2-62.2)	44.9 (19.8-86.4)	3.78 (3.47-4.08)	3.18 (3.01-3.36)
Central Europe	1 (0.5-1.8)	0.7 (0.4-1.3)	45.1 (20.1-84.3)	31 (14.1-58.5)	2 (1-3.5)	0.9 (0.4-1.5)	90.8 (42.4-166.9)	42.9 (19.6-79.5)	1.03 (0.86-1.19)	1.3 (1.13-1.47)
Central Latin America	2.1 (0.9-4)	2.8 (1.2-5.3)	74.8 (28.3-147.1)	88.6 (34.4-171.1)	6.7 (2.8-12.5)	3 (1.2-5.5)	224.2 (85.6-435.2)	95.1 (36.6-184)	-0.13 (-0.34-0.08)	0.21 (0-0.43)
Central Sub-Saharan Africa	0.5 (0.2-1)	3 (1.3-5.6)	16.6 (6.4-34.5)	77.2 (31.7-152.7)	1.2 (0.5-2.2)	3.1 (1.4-5.5)	44.9 (17.4-90.2)	86.5 (35.7-163.8)	-0.05 (-0.1-0)	0.35 (0.28-0.42)
East Asia	4.6 (2.1-8.4)	0.7 (0.3-1.2)	192.1 (83.7-357.3)	24.3 (11-43.1)	13.2 (6.1-23.2)	0.8 (0.4-1.3)	487.2 (208.5-922.4)	24.6 (10.9-45.8)	-0.03 (-0.24-0.18)	-0.37 (-0.54–0.21)
Eastern Europe	0.5 (0.2-0.9)	0.2 (0.1-0.4)	28.6 (12.6-54.2)	10.6 (4.7-20)	1.4 (0.6-2.5)	0.4 (0.2-0.7)	56.1 (25.8-102.9)	15.8 (7.3-29.5)	2.39 (1.72-3.06)	1.69 (1.49-1.9)
Eastern Sub-Saharan Africa	0.5 (0.2-1.2)	1 (0.4-2)	14.6 (5.5-32.3)	21.6 (8.3-47.3)	1.1 (0.4-2.3)	1 (0.4-2)	30.6 (11.6-68.1)	21.4 (8.2-45)	-0.1 (-0.14–0.06)	-0.08 (-0.11–0.05)
High-income Asia Pacific	1.4 (0.6-2.5)	0.8 (0.4-1.4)	64.2 (25.2-123.5)	32.1 (12.7-61.4)	2.5 (1.2-4.2)	0.4 (0.2-0.8)	132.1 (56.1-245.3)	31.8 (12-63)	-2.14 (-2.31–1.98)	-0.36 (-0.48–0.24)
High-income North America	4.6 (2.1-7.9)	1.3 (0.6-2.2)	160.6 (69-298.6)	46.3 (19.5-86.9)	6.3 (2.8-11.3)	0.9 (0.4-1.7)	293.4 (122.9-566.7)	49 (20.4-96)	-1.67 (-2.29–1.05)	0.5 (0.28-0.72)
North Africa and Middle East	4.9 (2.7-7.9)	3.6 (2-5.6)	179.4 (89.6-298.6)	106.4 (56.1-173.2)	14.4 (8.1-22.1)	3.9 (2.2-5.9)	685 (356.4-1111.5)	154 (82.7-245.6)	0.51 (0.36-0.65)	1.53 (1.4-1.66)
Oceania	0.2 (0.1-0.3)	7.4 (3.5-13.3)	5.3 (2.2-10.5)	182.2 (80.1-342.3)	0.6 (0.3-1.1)	11 (5.3-19.3)	20 (8.3-38.5)	281.4 (125.3-525.6)	1.14 (0.86-1.42)	1.32 (1.03-1.61)
South Asia	7.2 (3.5-12.8)	2 (1-3.4)	251.8 (113.6-461.3)	51.5 (24.8-91.5)	26.2 (13.1-43.7)	2.5 (1.3-4.1)	783.8 (374.1-1426.2)	62.2 (30.7-109.7)	0.95 (0.6-1.3)	1.14 (0.9-1.38)
Southeast Asia	3.8 (1.6-7.6)	1.9 (0.8-3.6)	112.7 (43.8-228.1)	47.4 (19.6-94.3)	12.9 (5.5-24.2)	2.5 (1.1-4.6)	403.3 (160.6-772.6)	69 (28.8-130.6)	0.96 (0.9-1.03)	1.25 (1.17-1.33)
Southern Latin America	0.2 (0.1-0.4)	0.5 (0.2-1)	6.1 (2.3-13.2)	13.4 (5-28.7)	0.6 (0.2-1.1)	0.7 (0.3-1.2)	20.1 (8.3-39.5)	24.1 (10-47.7)	1.26 (1-1.52)	2.31 (2.09-2.54)

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TABLE 1 Continued

characteristic	1990				2019				EAPC (1990-2019)	
	Death cases, n × 10^3 (95% UI)	ASMR per 10^5, n (95% UI)	DALYs, n × 10^3 (95% UI)	ASDR per 10^5, n (95% UI)	Death cases, n × 10^3 (95% UI)	ASMR per 10^5, n (95% UI)	DALYs, n × 10^3 (95% UI)	ASDR per 10^5, n (95% UI)	ASMR, n (95% CI)	ASDR, n (95% CI)
Region										
Southern Sub-Saharan Africa	1 (0.5-1.6)	4 (1.9-6.6)	28.9 (13.4-50.3)	105.3 (49.5-180.1)	3.1 (1.5-5.2)	6.7 (3.2-11.2)	86.9 (39.3-151.7)	160.8 (73.5-275.9)	2.43 (1.81-3.05)	2 (1.45-2.55)
Tropical Latin America	4.3 (2.5-6.3)	5.4 (3.2-7.9)	171.7 (93.7-263.8)	181 (101.5-273.5)	11.5 (6.9-16.5)	5 (3-7.1)	429.1 (248.4-650.9)	176 (101.6-266)	-0.24 (-0.3–0.17)	0.01 (-0.04-0.06)
Western Europe	9.5 (4.8-15.3)	1.6 (0.8-2.6)	268.5 (127.2-460.6)	46.1 (21.2-79.8)	13 (6.7-20.6)	1.1 (0.6-1.8)	476.4 (227.2-827.1)	54.1 (24.7-98)	-1.52 (-1.72–1.32)	0.22 (-0.02-0.45)
Western Sub-Saharan Africa	1.3 (0.6-2.4)	1.9 (0.8-3.5)	35.8 (15-70)	44.4 (19.3-84.7)	3.6 (1.5-6.5)	2.6 (1.1-4.5)	104.9 (43.2-200.9)	61.3 (26.2-113.4)	1.01 (0.81-1.21)	1.06 (0.89-1.24)

ASMR, age-standardized mortality rate; ASDR, age-standardized disability-adjusted life year rate; EAPC, estimated annual percentage change.

(Table 1, Figure 1A). Despite this rise in absolute numbers, the global ASMR showed a slight increase from 1.5 (95% UI: 0.8-2.5) to 1.6 (95% UI: 0.8-2.7) per 100 000, with an EAPC of 0.26 (95% CI: 0.13-0.39), indicating a modest rise in the mortality rate over the three decades (Table 1, Figure 1C).

There was a significant gender difference observed. The number of male fatalities attributed to type 2 diabetes due to physical inactivity increased from 18.9 thousand (95% UI: 8.5-33.8) in 1990 to 54 thousand (95% UI: 25.7-91.5) in 2019, and female deaths rose from 30.9 thousand (95% UI: 16-50.9) to 71.2 thousand (95% UI: 37-115.6). In males, the ASMR modestly increased from 1.4 to 1.6 per 100 000, whereas it remained relatively stable at 1.6 per 100 000 in females. A more pronounced EAPC was observed in males (0.51; 95% CI: 0.37-0.65) compared to females (0.09; 95% CI: -0.04-0.23), as shown in Table 1.

Regarding the SDI, high SDI regions witnessed a decrease in ASMR from 1.2 (95% UI: 0.6-2) per 100 000 in 1990 to 0.9 (95% UI: 0.4-1.5) per 100 000 in 2019, reflecting a significant reduction in mortality with an EAPC of -1.48 (95% CI: -1.81–1.15). The high-middle SDI regions observed a relatively constant ASMR, shifting marginally from 1.4 (95% UI: 0.7-2.2) per 100 000 to 1.3 (95% UI: 0.7-2) per 100 000 over the period 1990-2019, with an EAPC of -0.2 (95% CI: -0.33–0.07). Conversely, the low-middle SDI regions experienced the most notable ASMR increase, from 1.9 (95% UI: 1-3.2) per 100 000 in 1990 to 2.5 (95% UI: 1.3-4.1) per 100 000 in 2019, and an EAPC of 1.07 (95% CI: 0.91-1.24) (Table 1, Figure 1C). In the GBD regions, South Asia recorded the highest mortality in 2019 with 26.2 thousand deaths (95% UI: 13.1-43.7). The top ASMR in 2019 were in Oceania (11 per 100 000; 95% UI: 5.3-19.3) and Southern Sub-Saharan Africa (6.7 per 100 000; 95% UI: 3.2-11.2) (Table 1, Figure 2A). ASMR showed declining trends in regions like High-Income Asia Pacific and High-Income North America, while remaining stable in East Asia. However, ASMR were on the rise in Southern Sub-Saharan Africa and Central Asia, with Central Asia experiencing the sharpest increase (EAPC: 3.78; 95% CI: 3.47-4.08) (Table 1, Figure 2B).

Nationally, India recorded the highest count of type 2 diabetes fatalities attributable to physical inactivity, with numbers reaching 5238.9 (95% UI: 2483.5-9416) in 1990 and escalating to 19070.6 (95% UI: 9589.6-32291.6) by 2019. Qatar had the most elevated ASMR in 1990 at 19.3 (95% UI: 11.1-29) per 100 000, while Fiji reported the highest in 2019 at 29 (95% UI: 14.8-49.6) per 100 000. Conversely, Guatemala exhibited the lowest ASMR in 1990 (0.1 per 100 000; 95% UI: 0.1-0.4), and Ukraine had the lowest in 2019 (0.1 per 100 000; 95% UI: 0.1-0.2). Among 121 countries that experienced an increase in ASMR, Uzbekistan showed the most rapid growth (EAPC: 5.85; 95% CI: 5.26-6.44) (Figures 2A, B; Supplementary Table 1).

In 2019, the pattern of type 2 diabetes deaths due to physical inactivity in different age groups formed an inverted V-shape, with its peak in the 80-84 age group. The majority of these deaths were among individuals aged 60-89, predominantly in the middle and low-middle SDI regions (Figure 1E). Mortality rates in different age groups for patients with type 2 diabetes due to physical inactivity escalated with advancing age, particularly post the age of 80 (Figure 1G; Supplementary Figure 1A). On a global scale, the EAPC in mortality rates exhibited an inverted U-shaped relationship with age. Negative EAPC values were observed in the 25-29 and 70-74 age groups, while positive values were seen in the 30-64 and 75+ age groups. The sharpest decline in mortality was in the 25-29 age group, and the most significant increase was in the 40-44 age group. However, in low SDI regions, mortality rates rose consistently across all age groups (Supplementary Figure 1B).

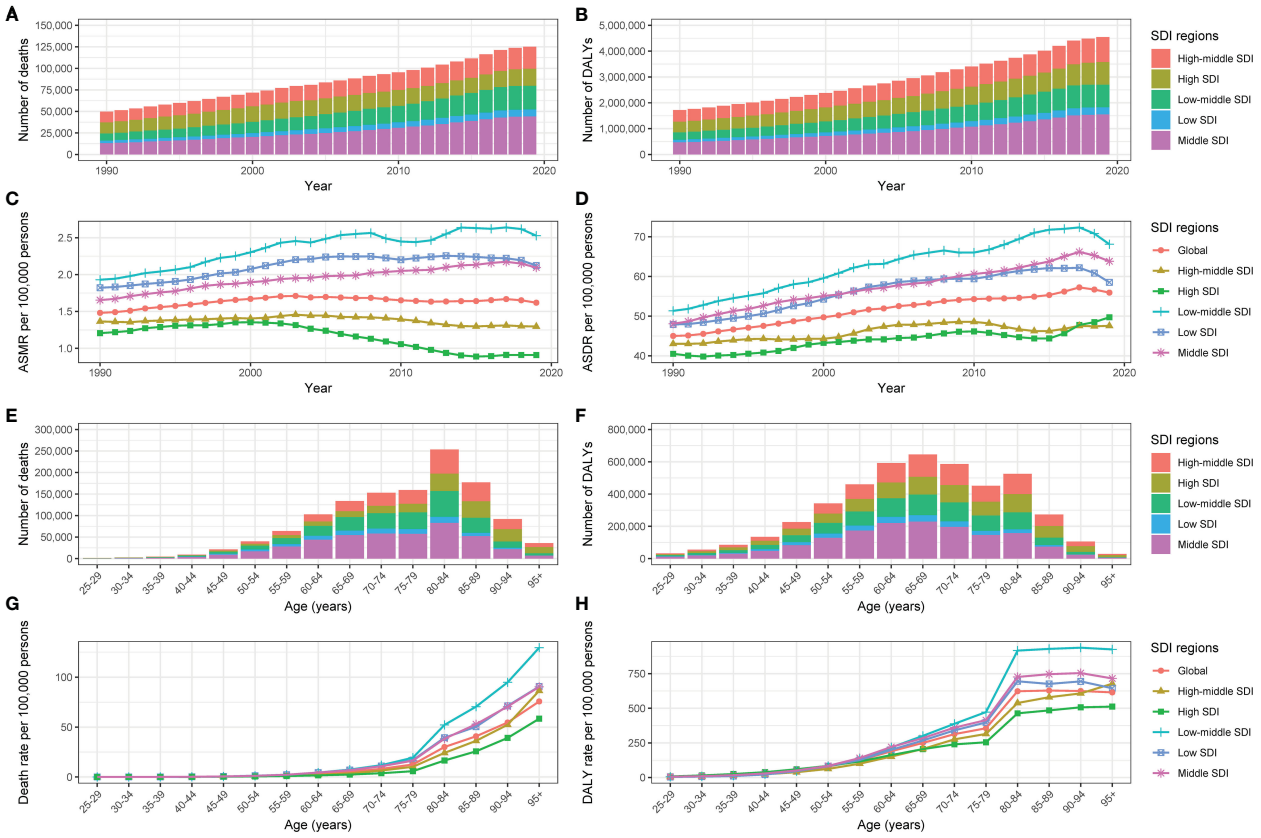

FIGURE 1
The type 2 diabetes burden attributable to physical inactivity by SDI region. The global **(A)** deaths, **(B)** DALYs, **(C)** ASMR and **(D)** ASDR of type 2 diabetes attributable to physical inactivity for all ages from 1990 to 2019. The global **(E)** deaths, **(F)** DALYs, **(G)** mortality rate and **(H)** DALYs rate of type 2 diabetes attributable to physical inactivity by age in 2019. SDI, Socio-demographic Index; ASMR, age-standardized mortality rate; DALYs, disability-adjusted life years; ASDR, age-standardized DALY rate.

Type 2 diabetes DALYs and ASDR associated with physical inactivity

Globally, the number of DALYs for type 2 diabetes associated with physical inactivity more than doubled from approximately 1.7 million (95% UI: 0.8-3.1) in 1990 to 4.5 million (95% UI: 2.2-8.0) in 2019 (Table 1, Figure 1B). Over the same period, the ASDR rose from 45 (95% UI: 21.3-79.5) per 100 000 to 55.9 (95% UI: 27.2-97.6) per 100 000, with an EAPC of 0.84 (95% CI: 0.78-0.89) (Table 1, Figure 1D).

A notable gender disparity was also observed for DALYs and ASDR. In males, DALYs increased from 691.5 thousand (95% UI: 288.5-1292.4) in 1990 to 2.0 million (95% UI: 0.9-3.7) in 2019. Over the same timeframe, female DALYs rose from 1.0 million (95% UI: 0.5-1.8) to 2.5 million (95% UI: 1.3-4.3). The ASDR slightly increased from 40.5 per 100 000 (95% UI: 17.9-73.9) to 54.3 per 100 000 (95% UI: 25-97.6) in males, while rising at a slower pace in females from 49.1 (95% UI: 24.1-84.6) per 100 000 to 57.5 (95% UI: 28.6-98.4) per 100 000. Males demonstrated a higher EAPC (0.99; 95% CI: 0.93-1.05) than females (0.73; 95% CI: 0.66-0.79) (Table 1).

Across SDI regions, high SDI areas exhibited a rise in DALYs from 420.3 thousand (95% UI: 187.2-765.9) in 1990 to 879 thousand (95% UI: 410.8-1574.4) by 2019. The ASDR also rose from 40.5 (95% UI: 17.8-74.8) per 100 000 to 49.7 (95% UI: 23-91.8) per 100 000 over the same timeframe, with an EAPC of 0.63 (95% CI: 0.54-0.73). High-middle SDI regions exhibited rises in DALYs from 445.7 thousand (95% UI: 213.5-759) in 1990 to 963.1 thousand (95% UI: 481.4-1662.4) in 2019, and in ASDRs from 43 (95% UI: 21.1-72.5) per 100 000 to 47.6 (95% UI: 23.8-81.9) per 100 000, with an EAPC of 0.39 (95% CI: 0.29-0.49). Similarly, the middle, low-middle, and low SDI regions all exhibited upward trends, with the fastest ASDR increase observed in low-middle SDI regions (EAPC: 1.19; 95% CI: 1.09-1.29) (Table 1, Figure 1D). Among GBD regions, the highest number of DALYs in 2019 occurred in South Asia with 783.8 thousand (95% UI: 374.1-1426.2), followed by North Africa and Middle East with 685 thousand (95% UI: 356.4-1111.5). The highest ASDR in 2019 shifted to Oceania (281.4 per 100 000; 95% UI: 125.3-525.6) and the Caribbean (184.1 per 100 000; 95% UI: 93.5-310.6).Considering the changes of ASDR in different regions over time, ASDR showed declining trends in regions including East Asia and High-Income Asia Pacific, while remaining relatively stable in Eastern Sub-Saharan Africa. However, ASDRs rose in other regions like Southern Latin America and Central Asia, with Central Asia having the fastest increase (EAPC: 3.18; 95% CI: 3.01-3.36) (Table 1, Figure 2D).

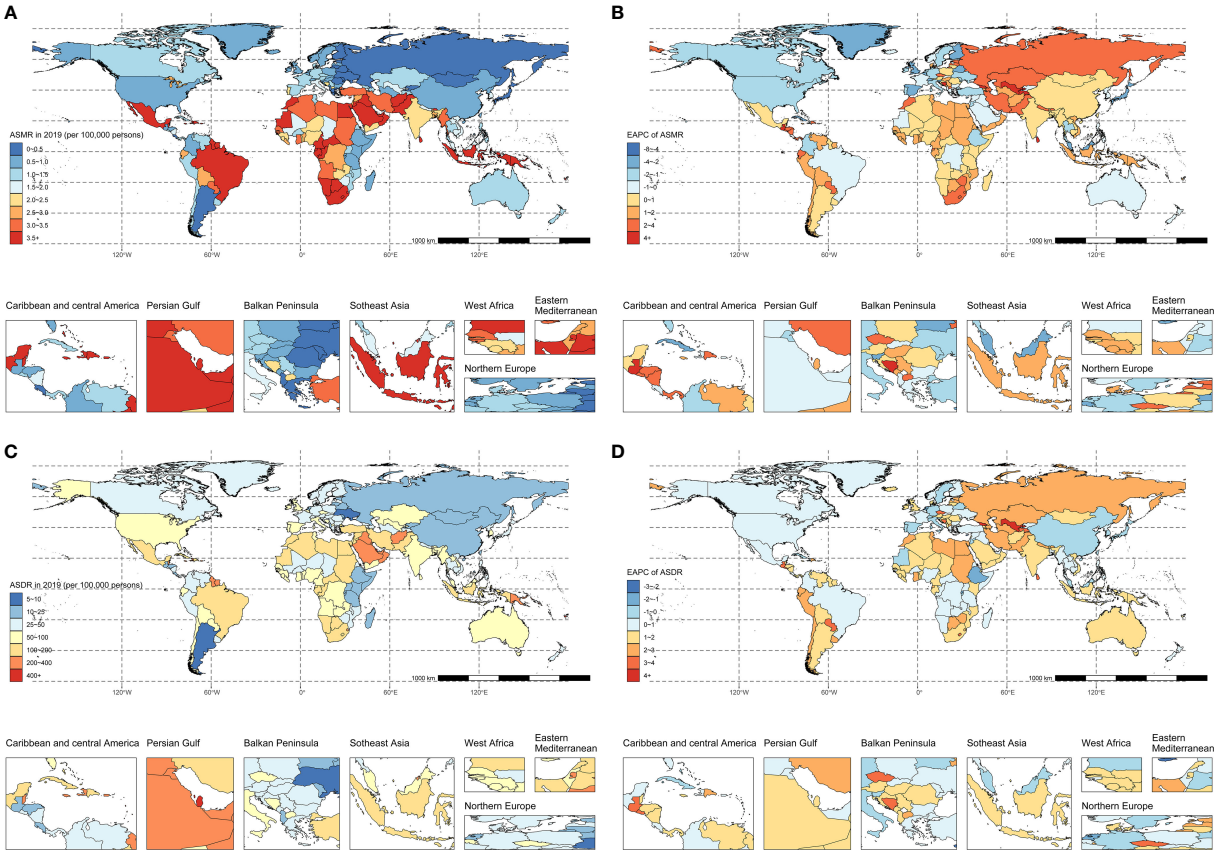

FIGURE 2
The spatial distribution of type 2 diabetes **(A)** ASMR, **(B)** the EAPC of ASMR, **(C)** ASDR, and **(D)** the EAPC of ASDR attributable to physical inactivity in 2019. ASMR, age-standardized mortality rate; EAPC, estimated annual percentage change; ASDR, age-standardized disability-adjusted life-years rate.

Nationally, India recorded the highest DALYs in 1990, totaling 194 thousand (95% UI: 86.5-355.8), while in 2019, India and China emerged as the leading countries in DALYs with 576.3 and 452.1 thousand, respectively. Trinidad and Tobago had the highest ASDR in 1990, at 447.2 (95% CI: 221.3-746) per 100 000, with Fiji leading in 2019, at 672.7 (95% CI: 317.8-1188.4) per 100 000. Guatemala and Mongolia consistently showed the lowest ASDR, recording 4.9 in 1990 and 11.4 in 2019 per 100 000. There were increases in ASDR trends in 157 countries and territories from 1990 to 2019, while 21 countries and territories exhibited downward trends in ASDR (Figures 2C, D; Supplementary Table 1).

In 2019, the number of DALYs for type 2 diabetes due to physical inactivity in different age groups reflected the observed pattern in mortality rates, peaking in the 65-69 age group (Figure 1F). In high and high-middle SD) regions, DALY rates consistently rose with increasing age. In contrast, in middle, low-middle, and low SDI regions, these rates initially surged until the age group of 80-84, followed by a slight variation in individuals aged over 85 (Figure 1H; Supplementary Figure 2A). The trend in the EAPC of DALY rates across different ages paralleled the EAPC trends seen in mortality rates (Supplementary Figure 2B).

Global Burden of Type 2 diabetes associated with physical inactivity by sex and age in 2019

Between 1990 and 2019, the global numbers of deaths and DALYs from type 2 diabetes associated with physical inactivity was higher among females than males (Figures 3A, B). While the ASMR was consistently greater in females, this disparity between male and female ASMR narrowed over the 30-year period. The 2019 data on deaths and DALYs in different age groups due to type 2 diabetes related to physical inactivity are depicted in Figures 3C, D. Similarly, the death and DALY counts were higher in females. Generally, the death rate for type 2 diabetes due to physical inactivity showed an upward trend for both sexes, with the DALY rate significantly increasing in the 75-84 age bracket, but stabilizing after 85 years of age.

Association between ASMR, ASDR of Type 2 diabetes and SDI values

The relationship between the ASMR for type 2 diabetes due to physical inactivity and the SDI values in various GBD regions

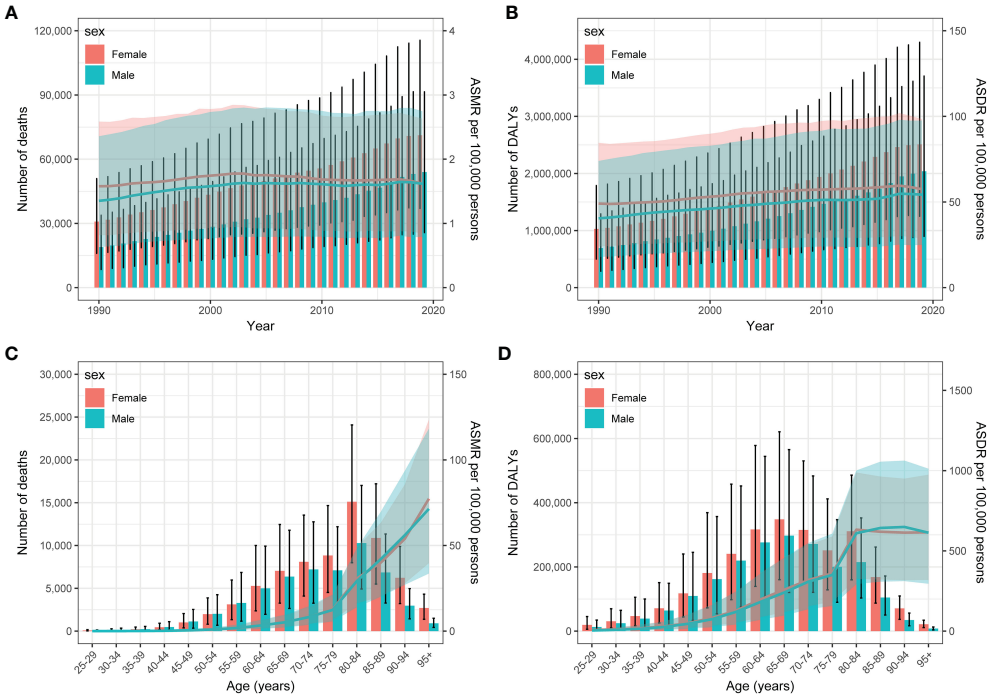

FIGURE 3
Year-specific numbers and rates of deaths **(A)** and DALYs **(C)**, and Age-specific numbers and rates of deaths **(B)** and DALYs **(D)** of type 2 diabetes attributable to physical inactivity by sex, in 2019. DALYs, disability-adjusted life years.

formed an M-shape. The ASMR initially rose until reaching an SDI of around 0.43, after which it declined as SDI values increased. In 2019, the EAPC in ASMR for type 2 diabetes due to physical inactivity showed a slight negative correlation with SDI, especially when SDI exceeded 0.65. Over the span from 1990 to 2019, more than half of the 204 countries analyzed displayed an upward ASMR trend (EAPC and 95% CI above 0) (Figure 4). A similar pattern was noted in the relationship between the age-standardized DALY rate, SDI values, and EAPC in the age-standardized DALY rate (Figure 5).

Discussion

In our research, we examined the spatial and temporal patterns of deaths and DALYs associated with physical inactivity and their influence on type 2 diabetes over the period from 1990 to 2019 in 204 countries. Our findings reveal a significant global increase in both deaths and DALYs attributable to type 2 diabetes related to physical inactivity, with deaths rising from 49.8 thousand to 125.2 thousand and DALYs more than doubling from 1.7 million to 4.5 million. While the ASMR showed a slight increase globally, notable geographical and socio-demographic disparities were observed. High SDI regions experienced a decrease in ASMR, contrasting with the stable or increasing rates in high-middle and low SDI regions. The rise in DALYs and disability rates was also more significant for males than females. The majority of deaths and DALYs attributable to physical inactivity occurred in those aged 60-89 years, predominantly in middle and low-middle SDI regions. These findings highlight the growing burden of type 2 diabetes due to insufficient physical activity across the globe, with an exceptionally high impact on elders and those in low to middle-income regions the urgent need for comprehensive public health strategies.

Type 2 diabetes, resulting from a progressive, non-autoimmune reduction in β-cell insulin secretion, often amid insulin resistance and metabolic syndrome, represents 90-95% of all diabetes cases. While the precise etiologies are unclear, type 2 diabetes does not involve the autoimmune destruction of β-cells or other known causes of diabetes (11). The complex interrelationship between physical inactivity and type 2 diabetes is rooted in intricate physiological mechanisms. Physical activity prevents type 2 diabetes through several physiological pathways (20–22). It can increase skeletal muscle glucose uptake to lower blood sugar levels. It also stimulates the release of adiponectin from adipose tissue, improving insulin sensitivity and mitigating insulin resistance. Regular physical activity aids weight control, reduces abdominal adiposity, and enhances insulin sensitivity, reducing type 2 diabetes risk (10). Activities of moderate intensity are categorized as having a MET value between 3 and 5.9, while those of vigorous intensity are characterized by a MET value of 6 or higher (23). Activities like walking briskly or raking the yard fall into the moderate-intensity category. On the other hand, vigorous intensity activities include actions such as jogging or running or lugging heavy groceries. Exercise guidelines suggests aiming for at least 150 minutes per week of aerobic exercise at a moderate-to-vigorous level, distributed across no less than three days weekly for patients with type 2 diabetes (24). Moreover, type 2 diabetes prevention efficacy varies

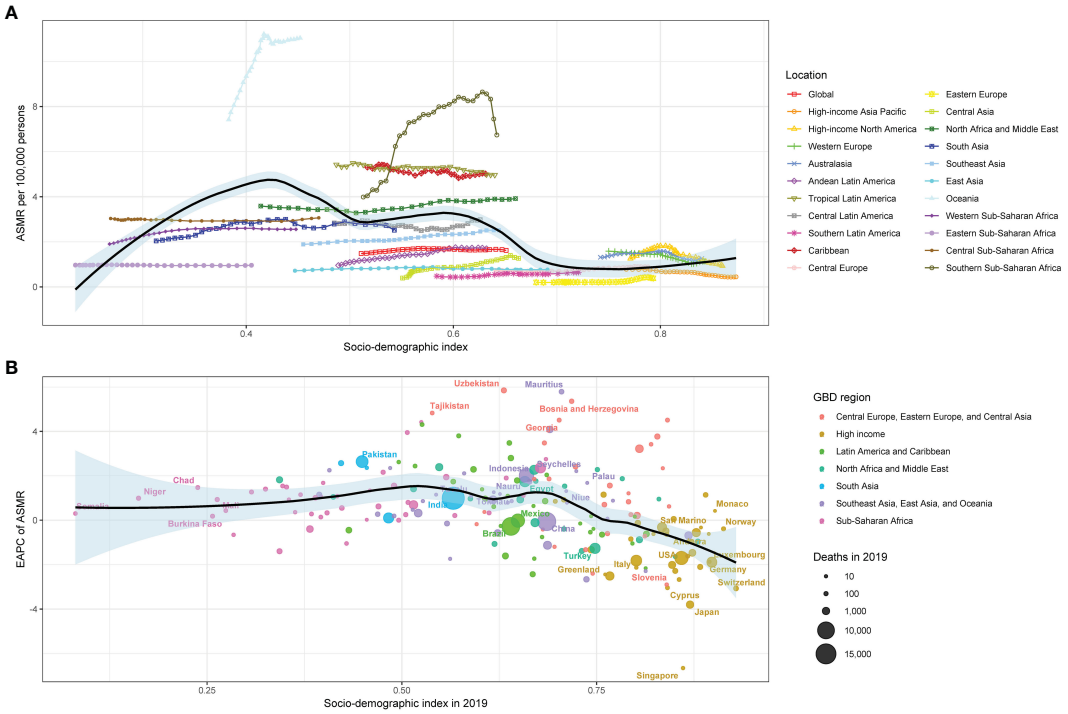

FIGURE 4
The relationship between type 2 diabetes **(A)** ASMR and SDI in 2019 by GBD region, **(B)** EAPC in ASMR and SDI in 2019 by Super GBD region. ASMR, age-standardized mortality rate; SDI, Socio-demographic Index; GBD, Global Burden of Disease Study; EAPC, estimated annual percentage change.

by exercise intensity, with studies showing moderate-intensity aerobic activity reduces type 2 diabetes incidence significantly more than lower-intensity exercise (25).

Among type 2 diabetes patients, different age-group mortality and DALYs attributable to physical inactivity exhibited pronounced increases with advancing age, peaking at 80-84 and 65-69 years, respectively. This trend signifies escalated vulnerability to the deleterious impacts of physical inactivity on type 2 diabetes in older populations. The exponential rise in different age-group mortality observed in type 2 diabetes patients, mainly those aged 80-84 years, due to physical inactivity can be attributed to an interplay of factors associated with aging. Advancing age leads to declines in skeletal muscle mass and quality, impairing glucose uptake capacity (26). Additionally, increased adiposity and upregulated proinflammatory cytokines from adipose tissue inhibit insulin signaling (27, 28). Deteriorating β-cell function also reduces insulin secretion with age (29). Collectively, these changes lead to decreased insulin sensitivity, which, if not compensated by physical activity, can precipitate hyperglycemia. Moreover, common age-related comorbidities like hypertension and atherosclerosis exacerbate insulin resistance and escalate mortality risk (30). Reduced mobility in elderly individuals limits their ability to perform aerobic exercise. Thus, elderly type 2 diabetes patients rely more heavily on regular physical activity to maintain glucose homeostasis than their younger counterparts. Insufficient activity may deteriorate glycemic control, increase complications, and heighten mortality risk (10). This highlights the importance of developing physical activity programs and glucose control measures tailored to cognitive and physical limitations in elderly individuals.

over the past 30 years, the burden of type 2 diabetes due to physical inactivity has saw a notable rise in both genders, with a more marked increase in men. Furthermore, although women have a greater burden of type 2 diabetes due to physical inactivity than men, the gap in ASMR and ASDR between the genders has recently been narrowing or reversing. The underlying reasons for this trend remain largely unexplored. Possible reasons include physiological differences between sexes, such as the impact of gestational diabetes in women (31), changes in estrogen levels, and patterns of fat distribution (32). Additionally, research has found that the prognosis for women with type 2 diabetes is worse than for men due to factors such as later diagnosis of type 2 diabetes in women, increased risk of cardiovascular disease (CVD) post-menopause, and deterioration of renal function in women (33). Societal norms and roles also impact physical activity levels. Men often engage more in physical labor or recreational sports, while women may have less time for such activities due to domestic responsibilities and caregiving roles. Research indicates unpaid domestic work and family duties can engender competing demands and chronic stress in women (34). Additionally, women generally have a higher intake of sugar, and diets with a high glycemic index tend to augment abdominal fat, particularly in sedentary women, in comparison to men (32). Similarly, a study on the burden of type 2 diabetes due to high body mass index (BMI) in China found a similar disease burden pattern (30), suggesting a synergistic effect of physical inactivity and high BMI in contributing to type 2 diabetes. Given

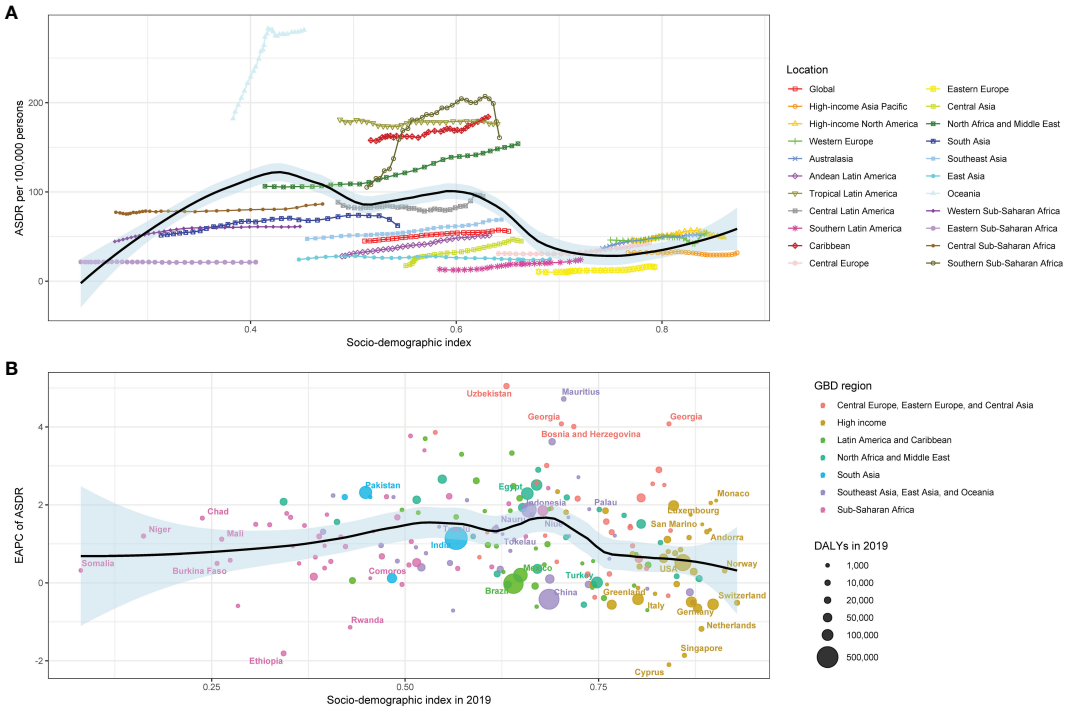

FIGURE 5
The relationship between type 2 diabetes **(A)** ASDR and SDI in 2019 by GBD region, **(B)** EAPC in ASDR and SDI in 2019 by Super GBD region. ASDR, age-standardized disability-adjusted life-years rate; SDI, Socio-demographic Index; GBD, Global Burden of Disease Study; EAPC, estimated annual percentage change.

the variations in disease prevalence, societal norms, and intervention responses, a gender-specific strategy is essential in public health measures aimed at reducing the impact of physical inactivity. This approach should focus on lessening the burden of type 2 diabetes in women and tackle the rising ASMR among men.

The SDI, encompassing per capita income, education levels, and fertility rates, plays a critical role in understanding the global and regional dynamics of type 2 diabetes linked to physical inactivity. Our study highlights a complex interplay between the SDI and the impact of type 2 diabetes due to physical inactivity. In many countries with medium and low-middle SDI, physical inactivity has led to a substantial disease burden with an increasing trend. Recognizing its status as the fourth most significant risk factor for numerous NCDs and premature death, the World Health Organization aims to decrease the rate of insufficient physical activity by 10% by 2025 to enhance NCD prevention and treatment (14). Numerous studies have shown that physical inactivity is notably higher among individuals with lower income and education levels (35). Workers with only primary education or no education were found to have approximately eight times less physical activity compared to their highly educated counterparts (36). This disparity may be attributed to individuals of higher socioeconomic status engaging more in leisure-time physical activities, whereas those from lower socioeconomic backgrounds often lack the resources for such activities or opportunities to be active in other areas (37). Implementing strategies like mass media exercise promotions, community and workplace support for physical activity, and enhancing infrastructures for exercise can boost activity levels (38). This suggests that local authorities, particularly in low SDI nations, should emulate high SDI countries in intensifying efforts to promote sports and improve lifestyle choices.

This study's inherent constraints stem from being a secondary analysis of the 2019 GBD data. Firstly, general limitations of the GBD study, including potential biases, are unavoidable and may lead to deviations from real-world figures. However, robust statistical methods were applied in the 2019 GBD study to address this issue. Secondly, GBD data are updated slowly, with the latest estimates only up to 2019, which may not capture the most current disease trends. Finally, estimating the type 2 diabetes burden attributable to physical inactivity did not account for complications arising from type 2 diabetes.

Conclusions

This study first delineated the burden and trends of type 2 diabetes attributable to physical inactivity. Low physical activity has inflicted a substantial disease burden on the global population, predominantly in middle-aged and elderly groups. These results underscore the importance of identifying physical inactivity as a modifiable risk factor for type 2 diabetes. They provide crucial guidance for crafting impactful public health strategies and policies to counteract the escalating mortality toll of this condition. Meantime, additional research is imperative, especially in light of the aging global population, to understand the reasons behind variations in type 2 diabetes across different regions and between genders.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Author contributions

XY: Conceptualization, Data curation, Investigation, Methodology, Software, Supervision, Writing – original draft, Writing – review & editing. JS: Formal analysis, Project administration, Validation, Writing – original draft. WZ: Conceptualization, Resources, Visualization, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2024.1343002/full#supplementary-material

References

1. Lee BX, Kjaerulf F, Turner S, Cohen L, Donnelly PD, Muggah R, et al. Transforming our world: implementing the 2030 agenda through sustainable development goal indicators. *J Public Health Policy* (2016) 37 Suppl 1:13–31. doi: 10.1057/s41271-016-0002-7

2. Sun H, Saeedi P, Karuranga S, Pinkepank M, Ogurtsova K, Duncan BB, et al. IDF Diabetes Atlas: Global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. *Diabetes Res Clin Pract* (2022) 183:109119. doi: 10.1016/j.diabres.2021.109119

3. Baena-Díez JM, Peñafiel J, Subirana I, Ramos R, Elosua R, Marín-Ibañez A, et al. Risk of cause-specific death in individuals with diabetes: A competing risks analysis. *Diabetes Care* (2016) 39(11):1987–95. doi: 10.2337/dc16-0614

4. Safiri S, Karamzad N, Kaufman JS, Bell AW, Nejadghaderi SA, Sullman MJM, et al. Prevalence, deaths and disability-adjusted-life-years (DALYs) due to type 2 diabetes and its attributable risk factors in 204 countries and territories, 1990-2019: results from the global burden of disease study 2019. *Front Endocrinol (Lausanne)* (2022) 13:838027. doi: 10.3389/fendo.2022.838027

5. Al-Mawali A. Non-communicable diseases: shining a light on cardiovascular disease, Oman's biggest killer. *Oman Med J* (2015) 30(4):227–8. doi: 10.5001/omj.2015.47

6. Carbone S, Del Buono MG, Ozemek C, Lavie CJ. Obesity, risk of diabetes and role of physical activity, exercise training and cardiorespiratory fitness. *Prog Cardiovasc Dis* (2019) 62(4):327–33. doi: 10.1016/j.pcad.2019.08.004

7. Guthold R, Stevens GA, Riley LM, Bull FC. Worldwide trends in insufficient physical activity from 2001 to 2016: a pooled analysis of 358 population-based surveys with 1.9 million participants. *Lancet Glob Health* (2018) 6(10):e1077–86. doi: 10.1016/S2214-109X(18)30357-7

8. Lee IM, Shiroma EJ, Lobelo F, Puska P, Blair SN, Katzmarzyk PT, et al. Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. *Lancet* (2012) 380(9838):219–29. doi: 10.1016/S0140-6736(12)61031-9

9. Ding D, Lawson KD, Kolbe-Alexander TL, Finkelstein EA, Katzmarzyk PT, van Mechelen W, et al. The economic burden of physical inactivity: a global analysis of major non-communicable diseases. *Lancet* (2016) 388(10051):1311–24. doi: 10.1016/S0140-6736(16)30383-X

10. ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, et al. 8. Obesity and weight management for the prevention and treatment of type 2 diabetes: standards of care in diabetes-2023. *Diabetes Care* (2023) 46(Suppl 1):S128–39. doi: 10.2337/dc23-S008

11. ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, et al. 2. Classification and diagnosis of diabetes: standards of care in diabetes-2023. *Diabetes Care* (2023) 46(Suppl 1):S19–40. doi: 10.2337/dc23-S002

12. Diseases GBD and Injuries C. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet* (2020) 396(10258):1204–22. doi: 10.1016/S0140-6736(20)30925-9

13. Collaborators GBDD. Global age-sex-specific fertility, mortality, healthy life expectancy (HALE), and population estimates in 204 countries and territories, 1950-2019: a comprehensive demographic analysis for the Global Burden of Disease Study 2019. *Lancet* (2020) 396(10258):1160–203. doi: 10.1016/S0140-6736(20)30977-6

14. Xu YY, Xie J, Yin H, Yang FF, Ma CM, Yang BY, et al. The Global Burden of Disease attributable to low physical activity and its trends from 1990 to 2019: An analysis of the Global Burden of Disease study. *Front Public Health* (2022) 10:1018866. doi: 10.3389/fpubh.2022.1018866

15. Collaborators GBDU-M. Global, regional, and national progress towards Sustainable Development Goal 3.2 for neonatal and child health: all-cause and cause-specific mortality findings from the Global Burden of Disease Study 2019. *Lancet* (2021) 398(10303):870–905. doi: 10.1016/S0140-6736(21)01207-1

16. Theodoropoulou E, Stavrou NAM, Karteroliotis K. Neighborhood environment, physical activity, and quality of life in adults: Intermediary effects of personal and psychosocial factors. *J Sport Health Sci* (2017) 6(1):96–102. doi: 10.1016/j.jshs.2016.01.021

17. Collaborators GBDRF. Global burden of 87 risk factors in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet* (2020) 396(10258):1223–49. doi: 10.1016/S0140-6736(20)30752-2

18. Yang X, Fang Y, Chen H, Zhang T, Yin X, Man J, et al. Global, regional and national burden of anxiety disorders from 1990 to 2019: results from the Global Burden of Disease Study 2019. *Epidemiol Psychiatr Sci* (2021) 30:e36. doi: 10.1017/S2045796021000275

19. Deng Y, Li H, Wang M, Li N, Tian T, Wu Y, et al. Global burden of thyroid cancer from 1990 to 2017. *JAMA Netw Open* (2020) 3(6):e208759. doi: 10.1001/jamanetworkopen.2020.8759

20. Narendran P, Solomon TP, Kennedy A, Chimen M, Andrews RC. The time has come to test the beta cell preserving effects of exercise in patients with new onset type 1 diabetes. *Diabetologia* (2015) 58(1):10–8. doi: 10.1007/s00125-014-3412-8

21. Park S, Hong SM, Lee JE, Sung SR. Exercise improves glucose homeostasis that has been impaired by a high-fat diet by potentiating pancreatic beta-cell function and mass through IRS2 in diabetic rats. *J Appl Physiol (1985)* (2007) 103(5):1764–71. doi: 10.1152/japplphysiol.00434.2007

22. Medina-Contreras JML, Colado-Velazquez J 3rd, Gomez-Viquez NL, Mailloux-Salinas P, Perez-Torres I, Aranda-Fraustro A, et al. Effects of topical capsaicin combined with moderate exercise on insulin resistance, body weight and oxidative

stress in hypoestrogenic obese rats. *Int J Obes (Lond)* (2017) 41(5):750–8. doi: 10.1038/ijo.2017.33

23. Piercy KL, Troiano RP, Ballard RM, Carlson SA, Fulton JE, Galuska DA, et al. The physical activity guidelines for americans. *JAMA* (2018) 320(19):2020–8. doi: 10.1001/jama.2018.14854

24. Mendes R, Sousa N, Almeida A, Subtil P, Guedes-Marques F, Reis VM, et al. Exercise prescription for patients with type 2 diabetes-a synthesis of international recommendations: narrative review. *Br J Sports Med* (2016) 50(22):1379–81. doi: 10.1136/bjsports-2015-094895

25. Jimenez-Maldonado A, Virgen-Ortiz A, Melnikov V, Rodriguez-Hernandez A, Gamboa-Dominguez A, Montero S, et al. Effect of moderate and high intensity chronic exercise on the pancreatic islet morphometry in healthy rats: BDNF receptor participation. *Islets* (2017) 9(1):1–10. doi: 10.1080/19382014.2016.1260796

26. Park MH, Kim DH, Lee EK, Kim ND, Im DS, Lee J, et al. Age-related inflammation and insulin resistance: a review of their intricate interdependency. *Arch Pharm Res* (2014) 37(12):1507–14. doi: 10.1007/s12272-014-0474-6

27. Paula FMM, Leite NC, Borck PC, Freitas-Dias R, Cnop M, Chacon-Mikahil MPT, et al. Exercise training protects human and rodent beta cells against endoplasmic reticulum stress and apoptosis. *FASEB J* (2018) 32(3):1524–36. doi: 10.1096/fj.201700710R

28. Sharif K, Watad A, Bragazzi NL, Lichtbroun M, Amital H, Shoenfeld Y. Physical activity and autoimmune diseases: Get moving and manage the disease. *Autoimmun Rev* (2018) 17(1):53–72. doi: 10.1016/j.autrev.2017.11.010

29. Kurauti MA, Soares GM, Marmentini C, Bronczek GA, Branco RCS, Boschero AC. Insulin and aging. *Vitam Horm* (2021) 115:185–219. doi: 10.1016/bs.vh.2020.12.010

30. Wu Y, Qin G, Wang G, Liu L, Chen B, Guan Q , et al. Physical activity, sedentary behavior, and the risk of cardiovascular disease in type 2 diabetes mellitus patients: the MIDiab study. *Engineering* (2023) 20:26–35. doi: 10.1016/j.eng.2022.05.013

31. Kim C, Newton KM, Knopp RH. Gestational Diabetes and the Incidence of Type 2 Diabetes: A systematic review. *Diabetes Care* (2002) 25(10):1862–8. doi: 10.2337/diacare.25.10.1862

32. Kautzky-Willer A, Harreiter J, Pacini G. Sex and gender differences in risk, pathophysiology and complications of type 2 diabetes mellitus. *Endocr Rev* (2016) 37 (3):278–316. doi: 10.1210/er.2015-1137

33. Stedman M, Whyte MB, Laing I, Fryer AA, Torres BM, Robinson A, et al. Failure to control conventional cardiovascular risk factors in women with type 2 diabetes might explain worse mortality. *Diabetes Metab Res Rev* (2023) 39(8):e3695. doi: 10.1002/dmrr.3695

34. Gisinger T, Azizi Z, Alipour P, Harreiter J, Raparelli V, Kublickiene K, et al. Sex and gender aspects in diabetes mellitus: Focus on access to health care and cardiovascular outcomes. *Front Public Health* (2023) 11:1090541. doi: 10.3389/fpubh.2023.1090541

35. Gupta R, Deedwania PC, Sharma K, Gupta A, Guptha S, Achari V, et al. Association of educational, occupational and socioeconomic status with cardiovascular risk factors in Asian Indians: a cross-sectional study. *PloS One* (2012) 7(8):e44098. doi: 10.1371/journal.pone.0044098

36. Reddy KS, Prabhakaran D, Jeemon P, Thankappan KR, Joshi P, Chaturvedi V, et al. Educational status and cardiovascular risk profile in Indians. *Proc Natl Acad Sci U.S.A* (2007) 104(41):16263–8. doi: 10.1073/pnas.0700933104

37. Stalsberg R, Pedersen AV. Are differences in physical activity across socioeconomic groups associated with choice of physical activity variables to report? *Int J Environ Res Public Health* (2018) 15(5). doi: 10.3390/ijerph15050922

38. Heath GW, Parra DC, Sarmiento OL, Andersen LB, Owen N, Goenka S, et al. Evidence-based intervention in physical activity: lessons from around the world. *Lancet* (2012) 380(9838):272–81. doi: 10.1016/S0140-6736(12)60816-2

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Role of remnant cholesterol in the relationship between physical activity and diabetes mellitus: an intermediary analysis

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Objective: The purpose of this investigation was to evaluate the potential link between physical activity (PA) and the heightened susceptibility to diabetes mellitus (DM), by examining whether remnant cholesterol (RC) might act as a mediator in this correlation.

Methods: The research utilized data from the National Health and Nutrition Examination Survey, spanning from 2005 to 2018. Various statistical analyses were conducted for continuous and categorical variables, including the *t*-test, ANOVA, and χ^2 test. Logistic regression was employed to analyze the association between PA and DM across three distinct models. Mediation analysis was also conducted to assess the potential mediation effects of RC.

Results: The study encompassed a total of 9,149 participants, and it was observed that individuals with DM exhibited lower levels of PA. Furthermore, PA levels were found to be associated with all participant characteristics except poverty income ratio, fasting blood glucose, and HOMA-IR ($p < 0.05$). After adjusting for covariates (Model 3), individuals with high PA levels demonstrated a decreased likelihood of developing DM compared to those in the low PA group (*OR*: 0.73, 95%*CI*: 0.54–0.99). A significant dose–response relationship was identified ($p < 0.05$). No interaction between PA and RC in relation to DM risk was detected, and RC was found to serve as a mediator in the connection between PA and DM. After considering covariates, the mediating effect of RC between PA and DM weakens.

Discussion: Our findings suggest that higher levels of PA are linked to a reduced risk of DM in U.S. adults, with RC likely playing a mediating role.

KEYWORDS

diabetes mellitus, physical activity, remnant cholesterol, intermediary analysis, National Health and Nutrition Examination Survey

Introduction

The global prevalence of diabetes mellitus (DM) is escalating, impacting more than 537 million adults aged 20–79 worldwide (1, 2) and emerging as a significant threat to global public health. Various factors, including gender, age, race, and obesity, contribute to the risk of DM (3, 4). In the context of evolving lifestyles, the role of physical activity (PA) as a crucial determinant of health has garnered substantial attention (5–7). Numerous studies indicate that elevated PA levels are associated with reduced glycosylated hemoglobin (HbA1c) levels and a lower incidence of DM (8–10). Moreover, leisure-time PA has demonstrated efficacy in mitigating the risk of DM-related mortality (11). These findings underscore the pivotal role of PA in diminishing the risk of DM.

Remnant cholesterol (RC) refers to the cholesterol content found in triglyceride-enriched lipoproteins, which include extremely low-density lipoprotein (VLDL), low-density lipoprotein (LDL), and chylomicron residues (12, 13). Research has indicated that RC particles are not only richer than LDL-C particles but also larger and carry a greater cholesterol load, suggesting that RC may pose a potential threat to pancreatic β cells (14). It is noteworthy that an increase in RC levels not only elevates the risk of major vascular diseases and complications related to DM but also heightens the risk of developing full-blown DM in individuals with prediabetes and high RC levels (15–19). Moreover, Hu et al. confirmed that RC was superior to LDL in the association with DM (20). Recent meta-analyses underscore the beneficial effects of higher levels of exercise on various health markers, including fasting blood glucose, total cholesterol, and triglycerides, suggesting the potential role of PA in regulating blood lipid levels (12, 13, 21). Additionally, as a component of the exercise regimen, resistance training has been associated with a decrease in RC levels, highlighting the connection between specific types of PA and lipid metabolism (22). Building upon the relationship between PA, RC, and DM mentioned above, we speculate that RC may play a crucial role in the complex interplay between PA and DM.

In this context, our study utilized data from the National Health and Nutrition Examination Survey (NHANES) to comprehensively examine the interrelationships among PA, RC, and DM. By investigating the potential mediating role of RC, we aim to offer valuable insights, furnish information for more effective interventions, and ultimately contribute to global efforts aimed at reducing the burden of DM.

Methods

Participants and study design

The current study conducted a retrospective cross-sectional analysis utilizing data from the continuous NHANES, spanning the years 2005 to 2018. NHANES is a comprehensive and multi-stage survey program, administered by the National Center for Health Statistics (NCHS) (23), with the primary objective of evaluating the health and nutritional status of the noninstitutionalized population in the United States. Commencing in 1999, continuous NHANES has consistently collected a wide array of information encompassing demographics, socioeconomic factors, dietary habits, and health-related data from selected participants, following a biennial cycle. The participation of individuals was contingent on obtaining informed consent, and the research protocol adhered to for conducting the NHANES survey had received approval from the NCHS Research Ethics Review Board. Comprehensive insights into the survey's design and response rate can be accessed on the NHANES official website[1] (24).

Among the 39,749 adult participants (aged≥20 years) who were included, we excluded the following: (1) pregnant participants ($n = 39,183$); (2) individuals lacking data regarding a diabetes diagnosis ($n = 39,038$); (3) those without available data on physical activity and remnant cholesterol ($n = 12,157$); (4) those without demographic data [gender, age, race, education level, marital status, health insurance, sleepiness level, alcohol consumption, smoking habits, poverty index ratio (PIR)] or dietary data [dietary inflammation index (DII)] or examination data [body mass index (BMI), glycosylated hemoglobin (HbA1c), fasting blood glucose (FBG), fasting serum insulin (FINS)] or medical history data [hypertension, cardiovascular disease (CVD)] ($n = 9,149$) (Figure 1).

Physical activity

Each participant completed a thorough physical activity questionnaire, which covered their physical activities during two different time frames: the past 30 days (from 2005 to 2006) and 1 week (from 2007 to 2018). This questionnaire collected detailed information about the activity type, frequency, intensity, and duration of physical activities conducted. Metabolic equivalent (MET) scores were calculated for specific activities based on activity type and intensity (25). These MET scores were then multiplied by the average duration and frequency of participation within the past 30 days or week. This multiplication resulted in the determination of MET minutes per 30 days (MET min/30d) or MET minutes per week (MET min/week) for each activity. Then we aggregated the MET minutes per 30 days or week for all reported activities. Subsequently, for participants who reported their physical activity monthly, we divided the total MET minutes per 30 days by 30 and then multiplied this figure by 7 to compute the total MET minutes per week for each participant. Afterward, participants were classified into three groups based on the standard scoring criteria of the International Physical Activity Questionnaire (IPAQ): low (<600 MET-min/week), moderate (600–3,000 MET-min/week), and high (≥3,000 MET-min/week) (26).

Diabetes mellitus

To define whether a participant had diabetes, this study utilized a combination of questionnaire data and examination data, and diabetes was judged to be present if any of the following criteria were met: (1) doctor told you have diabetes; (2) HbA1c (%) > 6.5; (3) fasting glucose (mmol/l) ≥ 7.0; (4) random blood glucose (mmol/l) ≥ 11.1; (5) two-hour OGTT blood glucose (mmol/l) ≥ 11.1; (6) Use of diabetes medication or insulin.

1 https://wwwn.cdc.gov/Nchs/Nhanes

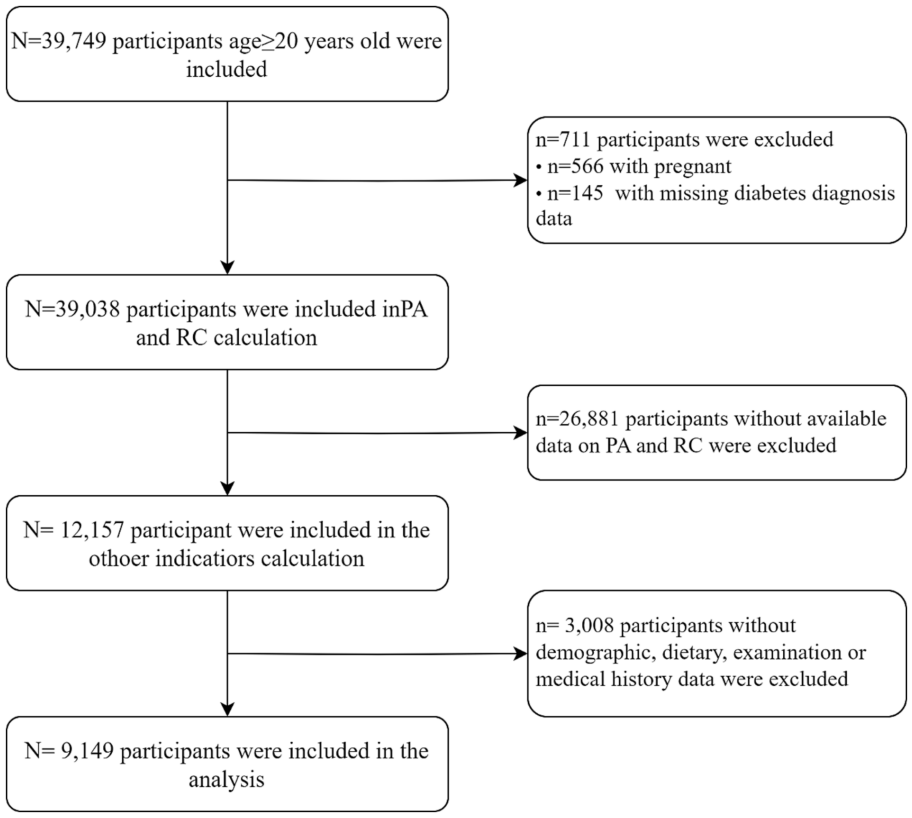

FIGURE 1
Flow chart of the study design.

Remnant cholesterol

RC (mmol/L) was calculated from a standard lipid profile of the patient in a fasting state as total cholesterol (TC) (mmol/L) minus LDL-C (mmol/L) minus HDL-C (mmol/L).

Study covariates

The included covariates included gender (female or male), education level (less than high school, completed high school and more than high school), race (non-Hispanic white, non-Hispanic black, Mexican American, and other), marital status (never married, married, and separated, divorced or widowed), age, PIR, health insurance (yes or no), cardiovascular disease (CVD), hypertension, body mass index (BMI), dietary inflammation index (DII), sleepiness level, alcohol use (former, never and now), smoking status (former, never and now), glycosylated hemoglobin (HbA1c), fasting blood glucose (FBG), HOMA-IR.

Statistical analysis

The recommended weighting method was used to analyze NHANES data. The baseline characteristics of the study population were reported as the mean (standard error, SEM) of continuous variables and the number (percentage) of categorical variables. We used the logistic regression model to estimate the *OR* and 95% *CI*.

For our main analysis, PA was included as a continuous variable, and due to its non-normal distribution, we opted for a logarithmic transformation to better suit our statistical analyses. We reported an estimate of the effect of 1-SD increase (z-score) in PA.

This method assumes a linear relationship between PA and DM. To check the hypothesis, we then used a multivariate restriction cubic spline and placed four nodes at the 5th, 35th, 65th, and 95th percentiles of the PA distribution nodes to provide a graphical representation. The spline curve allowed us to test whether there was a significant difference with the linear correlation. Finally, we categorized PA into three groups based on IPAQ criteria and considered the low group as the reference category in the logistic model.

Three models were proposed: the first model did not adjust for confounding factors; the second model was further adjusted for known risk factors for DM and potential confounding factors, such as age, gender, race, education level, marital status, smoking status, alcohol use, sleepiness level, health insurance status, PIR, BMI, CVD, DII, HbA1c, FBG, and HOMA-IR; and the third model further adjusted RC.

The interaction of PA and RC on the risk of DM was estimated by including a multiplication term between the two variables in the logistic model. Considering the statistical significance, we examined the association between PA and DM stratified by RC category. Regression-based mediation analysis was used to distinguish the

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TABLE 1 Weighted characteristics of the study population*.

Characteristics	Total (*n* = 9,149)	DM		χ^2/t	*P*-value
		No (*n* = 7,583)	Yes (*n* = 1,566)		
Age	45.65 ± 0.30	43.96 ± 0.32	57.45 ± 0.45	25.713	< 0.001
PIR	3.15 ± 0.04	3.17 ± 0.04	3.00 ± 0.06	−3.120	0.002
HbA1c	5.53 ± 0.01	5.34 ± 0.01	6.87 ± 0.05	29.074	< 0.001
FBG	5.77 ± 0.02	5.45 ± 0.01	8.07 ± 0.10	27.348	< 0.001
BMI	28.62 ± 0.11	28.03 ± 0.11	32.76 ± 0.25	17.620	< 0.001
DII	1.31 ± 0.04	1.29 ± 0.04	1.48 ± 0.08	2.553	0.012
HOMA-IR	3.19 ± 0.06	2.64 ± 0.04	6.97 ± 0.30	14.232	< 0.001
RC	0.59 ± 0.01	0.57 ± 0.01	0.74 ± 0.02	11.944	< 0.001
PA	4337.21 ± 103.00	4494.65 ± 110.31	3236.64 ± 157.62	−7.444	< 0.001
Ln PA	7.46 ± 0.03	7.49 ± 0.03	7.18 ± 0.04	−6.970	< 0.001
Gender				0.346	0.558
Male	4,825(51.90)	3,949(51.76)	876(52.91)		
Female	4,324(48.10)	3,634(48.24)	690(47.09)		
Race				9.558	< 0.001
Mexican American	1,327(7.30)	1,055(7.08)	272(8.80)		
Non-Hispanic white	4,281(71.10)	3,662(71.81)	619(66.18)		
Non-Hispanic black	1751(9.98)	1,383(9.51)	368(13.30)		
Other Hispanic and other	1790(11.61)	1,483(11.60)	307(11.72)		
Marital status				44.532	< 0.001
Married or living with partner	5,642(65.06)	4,646(64.77)	996(67.10)		
Widowed, divorced, or separated	1752(15.94)	1,333(14.84)	419(23.64)		
Never married	1755(19.00)	1,604(20.39)	151(9.26)		
Education level				19.512	< 0.001
Elementary and secondary education	1769(12.82)	1,363(12.25)	406(16.81)		
High school	2075(22.34)	1,670(21.51)	405(28.14)		
Bachelor degree or higher	5,305(64.84)	4,550(66.24)	755(55.05)		
Alcohol use				37.213	< 0.001
Never	1,045(9.05)	814(8.44)	231(13.30)		
Former	1,311(11.56)	965(10.61)	346(18.19)		
Now	6,793(79.39)	5,804(80.95)	989(68.51)		
Smoking status				18.573	< 0.001
Never	5,038(55.00)	4,245(55.58)	793(50.96)		
Former	2,279(25.34)	1760(24.11)	519(33.95)		
Now	1832(19.65)	1,578(20.31)	254(15.09)		
Hypertension				359.45	< 0.001
No	5,612(65.71)	5,112(70.40)	500(32.97)		
Yes	3,537(34.29)	2,471(29.60)	1,066(67.03)		
CVD				190.56	< 0.001
No	8,331(92.75)	7,082(94.45)	1,249(80.86)		
Yes	818(7.25)	501(5.55)	317(19.14)		
Sleepiness level				4.087	0.019
Short sleep	3,038(29.42)	2,476(28.92)	562(32.97)		

(Continued)

TABLE 1 (Continued)

Characteristics	Total (n = 9,149)	DM		χ^2/t	P-value
		No (n = 7,583)	Yes (n = 1,566)		
Normal	5,231(61.56)	4,398(62.22)	833(56.95)		
Long sleep	880(9.02)	709(8.87)	171(10.08)		
Health insurance				25.574	< 0.001
No	1984(17.07)	1753(17.86)	231(11.55)		
Yes	7,165(82.93)	5,830(82.14)	1,335(88.45)		
Two groups of RC				160.92	< 0.001
Low	4,579(50.39)	4,040(53.12)	539(31.33)		
High	4,570(49.61)	3,543(46.88)	1,027(68.67)		
Three groups of PA				16.036	< 0.001
Low	2,135(22.49)	1,699(21.78)	436(24.27)		
Moderate	3,623 (40.62)	2,954(40.10)	669(44.23)		
High	3,391(36.89)	2,930(38.12)	461(28.29)		

*Rate and mean ± standard deviation were weighted; t-test was used for continuous variable and χ^2-test was used for categorical variables.
PIR, poverty income ratio; HbA1c, glycosylated hemoglobin; FBG, fasting blood glucose; BMI, body mass index; DII, dietary Inflammatory Index; HOMA-IR, homeostatic model assessment for insulin resistance; RC, remnant cholesterol; PA, physical activity; Ln, natural logarithm; CVD, cardiovascular disease; DM, diabetes mellitus.

direct effect of adherence to PA on the risk of DM and the indirect effect mediated by RC. Three estimates were obtained as follows:

- Total effect, that is, the overall association between PA and the risk of DM, including the association mediated by RC;
- Direct effect, that is, the association between PA and DM risk, adjusted according to RC;
- Indirect effect, that is, the association between PA and DM risk mediated by RC.

In addition, to effectively understand the complex relationship between PA, RC, and DM, we used a counterfactual mediation model that allows exposure-medium interaction. All statistical analyses were performed using the software package R (The R Foundation).[2] A two-tailed p-value of <0.05 was considered statistically significant.

Results

Characteristics of participants

In this study, a grand total of 9,149 individuals were enlisted, out of which 1,566 participants were incorporated into the DM cohort. Compared with nondiabetics, participants with DM had higher rates of being non-Hispanic black, being divorced, widowed or separated, having less than a high school education, having previously consumed alcohol, having previously smoked cigarettes, having health insurance, and having hypertension and CVD. Participants with DM were also older and had higher HbA1c, FBG, BMI, DII, HOMA-IR, and RC. In addition, diabetic participants were less PA than non-diabetic participants. The general characteristics of the study population are shown in Table 1.

Characterization of participants according to PA

Characteristics of participants divided after grouping PA according to IPAQ criteria are shown in Table 2. Higher levels of PA were associated with lower age, HbA1c, RC, and DII. Meanwhile, compared with the group with low levels of PA, the intermediate and high-level groups had higher proportions of males, unmarried, current alcohol drinkers, and former smokers, and conversely, lower proportions of RC levels, suffering from hypertension, CVD, and DM.

Association between PA and DM

The findings from Table 3 indicate that there is an inverse relationship between PA and the risk of developing DM in the high-level group compared to the low-level group in Model 1 [*OR*: 0.59 (95% *CI*: 0.49–0.71)]. This negative association between high PA levels and DM risk is also observed in Model 2 and Model 3 [*OR*: 0.75 (95% *CI*: 0.58–0.98), *OR*: 0.76 (95% *CI*: 0.58–0.99), respectively]. Furthermore, a significant dose–response relationship is evident in all three models (P-trend <0.05). Similar results are obtained when analyzing a 1-SD increase in PA in Model 1 [*OR*: 0.82 (95% *CI*: 0.77–0.87)], Model 2 [*OR*: 0.82 (95% *CI*: 0.72–0.95)], and Model 3 [*OR*: 0.83 (95% *CI*: 0.72–0.96)]. In addition, we observed a positive correlation between high RC levels and DM risk in Model 1, Model 2, and Model 3 [*OR*: 2.48 (95% *CI*, 2.15–2.87), *OR*: 2.34 (95% *CI*: 1.99–2.75), *OR*: 1.29 (95% *CI*, 1.02–1.62)], and significant dose–response relationships (P trend < 0.05) were observed (Supplementary Table S1). In the results of the restricted cubic spline analysis in Figure 2, there is a non-linear relationship between PA and DM risk in the three models ($P_{\text{non-linear}} < 0.05$), indicating that after the inflection point, the DM risk gradually decreases with the increase of PA level (Figures 2A–C). In the restricted cubic spline analysis of RC and DM, there is a linear relationship in Model 3 (Figure 2D) ($P_{\text{non-linear}} > 0.05$). As RC increases, the risk of DM also gradually increases, and the same results were observed in Model 1 and Model 2 (Supplementary Figure S1).

2 http://www.R-project.org

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TABLE 2 Characteristics of adults aged 20 and above grouped by PA*.

Characteristics	Total (n = 9,149)	Three groups of PA			χ^2/t	P-value
		Low (n = 2,135)	Moderate (n = 3,623)	High (n = 3,391)		
Age	45.65 ± 0.30	48.78 ± 0.55	46.82 ± 0.41	42.47 ± 0.37	−7.305	< 0.001
PIR	3.15 ± 0.04	3.22 ± 0.06	3.32 ± 0.05	2.93 ± 0.04	−1.585	0.116
HbA1c	5.53 ± 0.01	5.57 ± 0.02	5.53 ± 0.02	5.52 ± 0.02	−2.278	0.025
FBG	5.77 ± 0.02	5.81 ± 0.04	5.77 ± 0.03	5.76 ± 0.03	−0.943	0.348
BMI	28.62 ± 0.11	29.09 ± 0.20	28.48 ± 0.15	28.49 ± 0.16	−3.033	0.003
DII	1.31 ± 0.04	1.52 ± 0.06	1.25 ± 0.05	1.26 ± 0.04	−3.816	< 0.001
HOMA-IR	3.19 ± 0.06	3.37 ± 0.11	3.21 ± 0.08	3.05 ± 0.08	−1.818	0.071
RC	0.59 ± 0.01	0.63 ± 0.01	0.59 ± 0.01	0.57 ± 0.01	−4.931	< 0.001
Gender					83.189	< 0.001
Male	4,825(51.90)	939(41.87)	1756(47.54)	2,130(62.82)		
Female	4,324(48.10)	1,196(58.13)	1867(52.46)	1,261(37.18)		
Race					8.251	< 0.001
Mexican American	1,327(7.30)	320(6.80)	433(5.68)	574(9.38)		
Non-Hispanic white	4,281(71.10)	988(71.18)	1759(73.14)	1,534(68.82)		
Non-Hispanic black	1751(9.98)	446(10.85)	641(8.65)	664(10.93)		
Other Hispanic and other	1790(11.61)	381(11.17)	790(12.54)	619(10.87)		
Marital status					11.888	< 0.001
Married or living with partner	5,642(65.06)	1,315(66.91)	2,280(66.15)	2047(62.73)		
Widowed, Divorced, or Separated	1752(15.94)	504(19.15)	672(15.71)	576(14.25)		
Never married	1755(19.00)	316(13.94)	671(18.14)	768(23.03)		
Education level					20.067	< 0.001
Elementary and secondary education	1769(12.82)	442(12.71)	564(10.08)	763(15.92)		
High school	2075(22.34)	514(23.89)	724(18.78)	837(25.31)		
Bachelor degree or higher	5,305(64.84)	1,179(63.40)	2,335(71.14)	1791(58.77)		
Alcohol use					6.639	< 0.001
Never	1,045(9.05)	295(10.96)	421(9.11)	329(7.83)		
Former	1,311(11.56)	381(14.63)	497(10.77)	433(10.55)		
Now	6,793(79.39)	1,459(74.41)	2,705(80.12)	2,629(81.62)		
Smoking status					8.424	< 0.001
Never	5,038(55.00)	1,208(57.66)	2072(56.82)	1758(51.37)		
Former	2,279(25.34)	540(24.17)	928(26.31)	811(24.99)		
Now	1832(19.65)	387(18.17)	623(16.86)	822(23.63)		
Hypertension					12.526	< 0.001
No	5,612(65.71)	1,175(60.26)	2,211(66.01)	2,226(68.72)		
Yes	3,537(34.29)	960(39.74)	1,412(33.99)	1,165(31.28)		
CVD					3.609	0.030
No	8,331(92.75)	1919(91.95)	3,269(92.16)	3,143(93.88)		
Yes	818(7.25)	216(8.05)	354(7.84)	248(6.12)		
Sleepiness level					3.802	0.005
Short sleep	3,038(29.42)	746(30.41)	1,109(26.83)	1,183(31.67)		

(Continued)

TABLE 2 (Continued)

Characteristics	Total (n = 9,149)	Three groups of PA			χ^2/t	P-value
		Low (n = 2,135)	Moderate (n = 3,623)	High (n = 3,391)		
Normal	5,231(61.56)	1,174(59.76)	2,164(64.43)	1893(59.50)		
Long sleep	880(9.02)	215(9.83)	350(8.74)	315(8.83)		
DM					16.036	< 0.001
No	7,583(82.88)	1,699(84.71)	2,954(86.37)	2,930(90.40)		
Yes	1,566(17.12)	436(15.29)	669(13.63)	461(9.60)		
Health insurance					26.560	< 0.001
No	1984(17.07)	415(16.01)	634(13.53)	935(21.62)		
Yes	7,165(82.93)	1720(83.99)	2,989(86.47)	2,456(78.38)		
Two groups of RC					11.932	< 0.001
Low	4,579(50.39)	985(45.75)	1808(49.72)	1786(53.96)		
High	4,570(49.61)	1,150(54.25)	1815(50.28)	1,605(46.04)		

*Rate and mean ± standard deviation were weighted; t-test was used for continuous variable and χ^2-test was used for categorical variables.
PIR, poverty income ratio; HbA1c, glycosylated hemoglobin; FBG, fasting blood glucose; BMI, body mass index; DII, dietary Inflammatory Index; HOMA-IR, homeostatic model assessment for insulin resistance; RC, remnant cholesterol; PA, physical activity; CVD, cardiovascular disease; DM, diabetes mellitus.

PA and DM risk stratified by RC category

According to Table 4, the occurrence of PA and DM was primarily observed in the high level of PA in Model 1, with a risk ratio of 0.66 (95% *CI*: 0.49–0.90) and 0.61 (95% *CI*: 0.48–0.77) respectively. Conversely, in Model 2, there was no correlation between PA and the risk of DM in either the low or high RC groups. Moreover, there was no significant interaction between PA and RC in relation to DM risk ($p > 0.05$).

The mediating role of RC

In Figure 3, it is evident that an increase in PA is linked to a reduction in the risk of DM. Approximately 30.79% of this effect can be attributed to a notable indirect impact associated with RC [*OR*: 0.992 (95%*CI*: 0.993, 0.996)] (as shown in Figure 3A). However, following the adjustment for covariates, the mediating effect of RC has weakened, accounting for 15.69%, and the indirect effect has statistical significance [*OR*: 0.999 (95%*CI*: 0.999, 1.000)] (Figure 3B). In addition, we will also include TG, HDL, LDL, and TC were used as mediating variables between PA and DM for mediation analysis. The results showed that after adjusting for covariates, TG had a mediating effect of 12.32%, HDL had a mediating effect of 8.92%, There is no mediating effect between LDL and TC (Supplementary Table S2).

Discussion

In this extensive cross-sectional investigation into the influence of PA and RC on the likelihood of developing DM, we uncovered several crucial findings. Initially, we noticed a distinct inverse relationship between PA and the risk of DM. As PA levels increase, the likelihood of developing DM steadily diminishes. This pattern is especially evident in Model 3, which establishes a consistent dose–response connection between PA and the risk of DM. In addition, we found a positive correlation between high RC levels and DM risk, and observed a significant linear dose–response relationship. In models not adjusted for covariates, it appeared that RC played a substantial mediating role in the relationship between PA and DM. When we consider the covariate adjusted model, the mediating effect of RC on the relationship between PA and DM weakens. Finally, our analysis of interactions demonstrated the absence of a substantial interaction between PA and RC regarding the risk of DM development.

Our results show that there is a consistent negative correlation between higher levels of PA and the risk of DM. The observation results of the dose–response relationship between the three models support this point, indicating that the risk of DM decreases with the increase of PA. This finding is consistent with the existing literature, which emphasizes the protective role of regular PA in the prevention and management of DM. For instance, a study on the risk of DM among Kurdish populations in Iran identified PA as a protective factor, with higher daily PA levels associated with a reduced incidence of DM (27). Similarly, Brož et al. found that both aerobic and muscle-strengthening exercises were less frequent in the DM group in contrast to the non-diabetes group (28). In the Czech population, aged 25–64, a higher prevalence of DM was observed among individuals with low levels of PA. In addition, restricted cubic spline analysis reveals a nonlinear relationship between PA and DM risk, indicating the existence of a turning point beyond which the protective effect of PA becomes more significant. This nonlinear model emphasizes the importance of reaching a certain PA threshold to maximize the benefits of reducing the risk of DM.

In our study, compared with the non-diabetes group, the RC level of DM patients is higher, and there is a significant linear relationship between RC and DM. The higher RC level is associated with the increased risk of DM. Some studies also support the correlation between RC and DM from the side. A DM prevention cohort study (22) shows that the RC concentration in the pre diabetes group is significantly higher than that in the normal population. Additionally, in a single-center cohort study (29), it was found that elevated RC

levels were independently linked to a higher risk of developing new DM (*HR*: 2.44, 95% *CI*: 1.50–3.89). It is worth noting that, Numerous research endeavors have corroborated the strong connection between PA and RC. In a controlled experiment with randomization (22), the experimental group witnessed a decline in non-high-density lipoprotein cholesterol levels, specifically RC, subsequent to engaging in resistance training. And the RC level of high-intensity occupational activities is lower than that of low-intensity non occupational activities (30). Another study also found that the RC levels of subjects who met the PA guidelines for PA intensity were lower than those who did not meet the PA guidelines (31). Overall, regular moderate intensity PA has been shown to regulate RC by preventing an increase in LDL cholesterol and triglyceride levels (32). Our findings also support this perspective, which will contribute to a better understanding of the intricate association between PA, RC, and DM. The mediation analysis indicates that approximately 30.79% of the protective effect of PA on DM risk can be attributed to a notable indirect impact associated with RC. This implies that the beneficial effects of PA on DM may, in part, operate through the modulation of residual cholesterol levels. Research has shown that RC directly or indirectly regulates insulin sensitivity by affecting lipid metabolism (33, 34), and high levels of PA have been shown to be associated with improving lipid metabolism and increasing insulin sensitivity in different populations (35–37), The increase in RC levels may interfere with normal lipid metabolism, leading to disruption of insulin signaling and thus increasing the risk of DM. The mediating role of RC may also involve the regulation of inflammation and oxidative stress (38, 39), and PA has been proven to have a positive impact on combating inflammation and reducing

TABLE 3 DM risk based on PA grouping*.

Three groups of PA	Model 1 *OR* (95% *CI*)	Model 2 *OR* (95% *CI*)	Model 3 *OR* (95% *CI*)
Low	Reference		
Moderate	0.87(0.72–1.06)	1.09(0.88–1.35)	1.09(0.88–1.36)
High	0.59(0.49–0.71)	0.75(0.58–0.98)	0.76(0.58–1.00)
P-trend	<0.001	0.032	0.042
For 1-SD increase	0.82(0.77–0.87)	0.821(0.72–0.95)	0.83(0.72–0.96)

*All estimates were weighted.

PA, physical activity; DM, diabetes mellitus; OR, odds ratio; CI, confidence interval. Model 1: Did not adjust any covariates; Model 2: Adjusted for age, PIR, FBG, BMI, DII, HOMA-IR, gender, race, marital status, education level, alcohol use; smoking status, hypertension, CVD, sleepiness level and health insurance; Model 3: Adjusted for age, PIR, FBG, BMI, DII, HOMA-IR, gender, race, marital status, education level, alcohol use; smoking status, hypertension, CVD, sleepiness level and health insurance, and RC; For 1-SD increase: Using PA with natural logarithms.

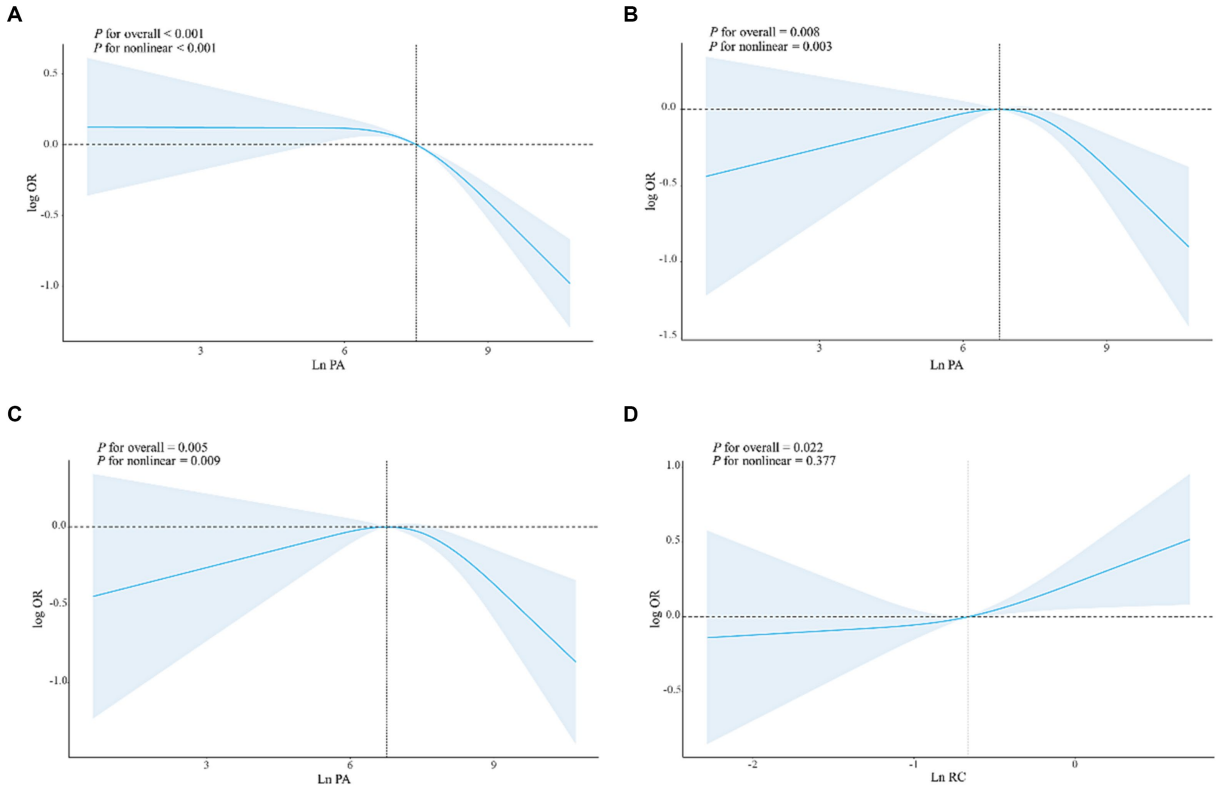

FIGURE 2
The dose–response relationships of PA/RC with DM in all participants. Results were from restricted cubic spline models. **(A)** The dose–response relationship between PA and DM without adjusting for any covariates. **(B)** The dose–response relationship between PA and DM adjusted for age, PIR, FBG, BMI, DII, HOMA-IR, gender, race, marital status, education level, alcohol use, smoking status, hypertension, CVD, sleepiness level, and health insurance. **(C)** The dose–response relationship between PA and DM adjusted for age, PIR, FBG, BMI, DII, HOMA-IR, gender, race, marital status, education level, alcohol use; smoking status, hypertension, CVD, sleepiness level and health insurance, and RC. **(D)** The dose–response relationship between RC and DM adjusted for age, PIR, FBG, BMI, DII, HOMA-IR, gender, race, marital status, education level, alcohol use; smoking status, hypertension, CVD, sleepiness level and health insurance, and PA.

TABLE 4 Risk of DM by three groups of PA stratified according to two groups of RC*.

Two groups of RC	Three groups of PA	Model 1	*P*-value	Model 2	*P*-value
		OR (95% *CI*)		*OR* (95% *CI*)	
Low	Low	Reference		Reference	
	Moderate	1(0.75–1.34)	0.992	1.43(0.93–2.18)	0.010
	High	0.66(0.49–0.90)	0.009	0.841(0.52–1.33)	0.447
	P-trend	0.003		0.302	
High	Low	Reference		Reference	
	Moderate	0.86(0.67–1.10)	0.225	0.93(0.69–1.27)	0.656
	High	0.61(0.48–0.77)	< 0.001	0.70(0.49–1.01)	0.054
	P-trend	<0.001		0.052	
$P_{interaction}$		0.733		0.270	

*All estimates were weighted. PA, physical activity; RC, remnant cholesterol; DM, diabetes mellitus; OR, odds ratio; CI, confidence interval; $P_{interaction}$ is the value of interaction between PA and RC on DM. Molde 1: Did not adjust any covariates; Molde 2: Adjusted for age, PIR, FBG, BMI, DII, HOMA-IR, gender, race, marital status, education level, alcohol use; smoking status, hypertension, CVD, sleepiness level and health insurance.

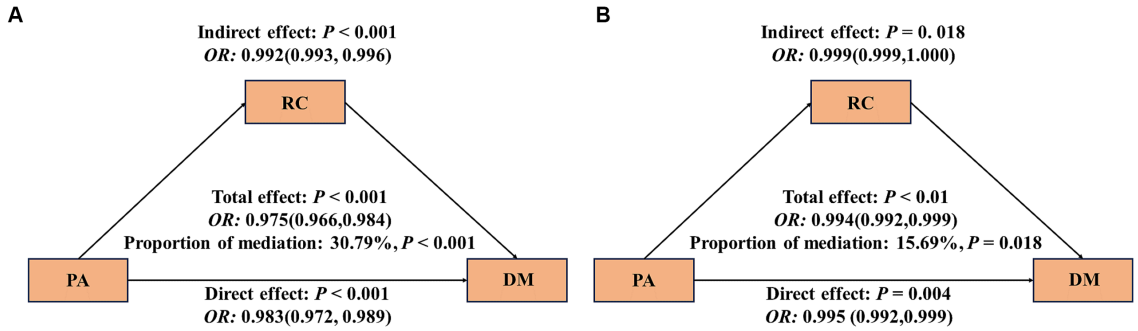

FIGURE 3
Mediating effect of RC between PA and DM. The 95% *CI* of these estimates was computed using the bootstrap method (1,000 samples); **(A)** did not adjust any covariates; **(B)** was adjusted for age, PIR, FBG, BMI, DII, HOMA-IR, gender, race, marital status, education level, alcohol use; smoking status, hypertension, CVD, sleepiness level and health insurance.

oxidative stress (40–42). The accumulation of RC may trigger inflammatory reactions and exacerbate oxidative stress, leading to the development of insulin resistance and DM.

It is worth noting that after adjusting the covariates, the mediating effect of RC decreased from the original 30.79–15.69%. It may be that the role of RC in the pathogenesis of DM is affected by other covariates. Some studies have found that BMI, smoking, PA, etc. play a mediating role between education level and type 2 diabetes (43). In a mediation analysis of DM neuropathy (44), HbA1c plays a strong mediating role. In addition, albumin, HDL-C, TG, apolipoprotein A, and C-reactive protein also play a mediating role. In our study, we also found that TG had a mediating effect of 12.32% and HDL had a mediating effect of 8.92%, but LDL and TC did not show a mediating effect. Further research is needed to explain these interactions. In addition, the interaction between PA and RC on DM risk is not significant (Table 4), and in stratified analysis, regardless of RC stratification, the effect between PA and DM risk is consistent. This means that our results are robust.

This study has several advantages. It utilizes a representative and extensive sample of data, and it examines the association between PA and DM using multiple analytical approaches. Additionally, it investigates the potential role of RC in this association. Our study reveals a distinct and independent correlation between PA and the risk of DM, Importantly, there is no interaction between RC and PA when it comes to the risk of DM. In other words, RC does not influence the relationship between PA and DM. This finding has significant implications for clinical practice and public health. By increasing PA, a modifiable factor, we can effectively prevent or alleviate symptoms of DM. Nevertheless, it is crucial to acknowledge the limitations of our research. Firstly, our study measures PA as a cumulative sum of all physical activities in daily life. It does not distinguish between different types of PA, such as vigorous work activity, recreational activities, or moderate work and recreational activities, including walking or cycling for transportation (45). Consequently, we are unable to determine the specific impact of each type of PA on DM. Secondly, the results of our study are derived from American adults and may not accurately reflect the true situation of other populations. Additionally, as a cross-sectional study, our research cannot establish a causal relationship between PA and DM. It is imperative to conduct further prospective on-site intervention studies to provide stronger evidence on the association between PA and DM.

Overall, this study provides evidence supporting the protective role of PA in reducing DM risk, while emphasizing the potential mediating role of RC. Understanding the complex relationship among

PA, RC and DM risks is crucial for developing targeted interventions and personalized DM prevention and management methods.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

Ethical approval was not required for the study involving humans in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and the institutional requirements.

Author contributions

ZY: Data curation, Formal analysis, Writing – original draft. HC: Data curation, Formal analysis, Writing – original draft. FL: Methodology, Visualization, Writing – review & editing. JZ: Investigation, Writing – review & editing. ShiW: Formal analysis, Methodology, Writing – review & editing. ShuW: Formal analysis, Investigation, Visualization, Writing – review & editing. YC: Formal analysis, Methodology, Validation, Writing – review & editing. ZM: Data curation, Resources, Writing – review & editing. LL: Investigation, Validation, Writing – review & editing. DK: Supervision, Writing – review & editing. YD: Resources, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2024.1322244/full#supplementary-material

References

1. Khan MAB, Hashim MJ, King JK, Govender RD, Mustafa H, Al KJ. Epidemiology of type 2 diabetes – global burden of disease and forecasted trends. *J Epidemiol Glob Health*. (2020) 10:107–11. doi: 10.2991/jegh.k.191028.001

2. Magliano DJ, Boyko EJ (2021). *IDF Diabetes Atlas*. Available at: https://pubmed.ncbi.nlm.nih.gov/35914061/

3. Nguyen NT, Nguyen XMT, Lane J, Wang P. Relationship between obesity and diabetes in a US adult population: findings from the National Health and nutrition examination survey, 1999–2006. *Obes Surg*. (2011) 21:351–5. doi: 10.1007/s11695-010-0335-4

4. Lindström J, Tuomilehto J. The diabetes risk score: a practical tool to predict type 2 diabetes risk. *Diabetes Care*. (2003) 26:725–31. doi: 10.2337/diacare.26.3.725

5. Weinstein AR, Sesso HD, Lee IM, Cook NR, Manson JE, Buring JE, et al. Relationship of physical activity vs body mass index with type 2 diabetes in women. *JAMA*. (2004) 292:1188–94. doi: 10.1001/jama.292.10.1188

6. Li Y, Schoufour J, Wang DD, Dhana K, Pan A, Liu X, et al. Healthy lifestyle and life expectancy free of cancer, cardiovascular disease, and type 2 diabetes: prospective cohort study. *BMJ*. (2020) 368:l6669. doi: 10.1136/bmj.l6669

7. Balk EM, Earley A, Raman G, Avendano EA, Pittas AG, Remington PL. Combined diet and physical activity promotion programs to prevent type 2 diabetes among people at increased risk: a systematic review for the community preventive services task force. *Ann Intern Med*. (2015) 163:437–51. doi: 10.7326/M15-0452

8. Gay JL, Buchner DM, Schmidt MD. Dose-response association of physical activity with HbA1c: intensity and bout length. *Prev Med*. (2016) 86:58–63. doi: 10.1016/j.ypmed.2016.01.008

9. Xu F, Earp JE, Adami A, Weidauer L, Greene GW. The relationship of physical activity and dietary quality and diabetes prevalence in US adults: findings from NHANES 2011–2018. *Nutrients*. (2022) 14:3324. doi: 10.3390/nu14163324

10. Zhao F, Wu W, Feng X, Li C, Han D, Guo X, et al. Physical activity levels and diabetes prevalence in US adults: findings from NHANES 2015–2016. *Diabetes Ther*. (2020) 11:1303–16. doi: 10.1007/s13300-020-00817-x

11. Boyer WR, Ehrlich SF, Crouter SE, Churilla JR, Fitzhugh EC. Leisure-time aerobic physical activity and the risk of diabetes-related mortality: an analysis of effect modification by race-ethnicity. *J Diabetes Complicat*. (2021) 35:107763. doi: 10.1016/j.jdiacomp.2020.107763

12. Twickler TB, Dallinga-Thie GM, Cohn JS, Chapman MJ. Elevated remnant-like particle cholesterol concentration: a characteristic feature of the atherogenic lipoprotein phenotype. *Circulation*. (2004) 109:1918–25. doi: 10.1161/01.CIR.0000125278.58527.F3

13. Jørgensen AB, Frikke-Schmidt R, West AS, Grande P, Nordestgaard BG, Tybjærg-Hansen A. Genetically elevated non-fasting triglycerides and calculated remnant cholesterol as causal risk factors for myocardial infarction. *Eur Heart J*. (2013) 34:1826–33. doi: 10.1093/eurheartj/ehs431

14. Sokooti S, Flores-Guerrero JL, Heerspink HJL, Connelly MA, Bakker SJL, Dullaart RPF. Triglyceride-rich lipoprotein and LDL particle subfractions and their association with incident type 2 diabetes: the PREVEND study. *Cardiovasc Diabetol*. (2021) 20:156. doi: 10.1186/s12933-021-01348-w

15. Yu D, Wang Z, Zhang X, Qu B, Cai Y, Ma S, et al. Remnant cholesterol and cardiovascular mortality in patients with type 2 diabetes and incident diabetic nephropathy. *J Clin Endocrinol Metab*. (2021) 106:3546–54. doi: 10.1210/clinem/dgab533

16. Schaefer EJ, McNamara JR, Shah PK, Nakajima K, Cupples LA, Ordovas JM, et al. Elevated remnant-like particle cholesterol and triglyceride levels in diabetic men and women in the Framingham offspring study. *Diabetes Care*. (2002) 25:989–94. doi: 10.2337/diacare.25.6.989

17. Jansson Sigfrids F, Dahlström EH, Forsblom C, Sandholm N, Harjutsalo V, Taskinen MR, et al. Remnant cholesterol predicts progression of diabetic nephropathy and retinopathy in type 1 diabetes. *J Intern Med*. (2021) 290:632–45. doi: 10.1111/joim.13298

18. Jørgensen PG, Jensen MT, Biering-Sørensen T, Mogelvang R, Galatius S, Fritz-Hansen T, et al. Cholesterol remnants and triglycerides are associated with decreased myocardial function in patients with type 2 diabetes. *Cardiovasc Diabetol*. (2016) 15:137. doi: 10.1186/s12933-016-0454-x

19. Xu Y, Wang L, He J, Bi Y, Li M, Wang T, et al. Prevalence and control of diabetes in Chinese adults. *JAMA*. (2013) 310:948–59. doi: 10.1001/jama.2013.168118

20. Hu X, Liu Q, Guo X, Wang W, Yu B, Liang B, et al. The role of remnant cholesterol beyond low-density lipoprotein cholesterol in diabetes mellitus. *Cardiovasc Diabetol*. (2022) 21:117. doi: 10.1186/s12933-022-01554-0

21. Pan B, Ge L, Xun YQ, Chen YJ, Gao CY, Han X, et al. Exercise training modalities in patients with type 2 diabetes mellitus: a systematic review and network meta-analysis. *Int J Behav Nutr Phys Act*. (2018) 15:72. doi: 10.1186/s12966-018-0703-3

22. Sarin HV, Ahtiainen JP, Hulmi JJ, Ihalainen JK, Walker S, Küüsmaa-Schildt M, et al. Resistance training induces antiatherogenic effects on metabolomic pathways. *Med Sci Sports Exerc*. (2019) 51:1866–75. doi: 10.1249/MSS.0000000000002003

23. National Center for Health Statistics (NCHS). *NHANES survey methods and analytic guidelines*. Available at: https://wwwn.cdc.gov/nchs/nhanes/analyticguidelines.aspx

24. Ainsworth BE, Haskell WL, Whitt MC, Irwin ML, Swartz AM, Strath SJ, et al. Compendium of physical activities: an update of activity codes and MET intensities. *Med Sci Sports Exerc*. (2000) 32:S498–516. doi: 10.1097/00005768-200009001-00009

25. IPAQ Research Committee. *Guidelines for data processing and analysis of the international physical activity questionnaire (IPAQ) – short and long forms*. Available at: https://www.physio-pedia.com/images/c/c7/Quidelines_for_interpreting_the_IPAQ.pdf

26. Safari-Faramani R, Rajati F, Tavakol K, Hamzeh B, Pasdar Y, Moradinazar M, et al. Prevalence, awareness, treatment, control, and the associated factors of diabetes in an Iranian Kurdish population. *J Diabetes Res*. (2019) 2019:1–9. doi: 10.1155/2019/5869206

27. Dorner TE, Lackinger C, Haider S, Stein KV. Lifestyle parameters in patients with diabetes mellitus and in the general adult population-trends over five years: results of the Austrian National Health Interview Series. *Int J Environ Res Public Health*. 202. 18:9910. doi: 10.3390/ijerph18189910

28. Brož J, Malinovská J, Nunes MA, Kučera K, Rožeková K, Žejglicová K, et al. Prevalence of diabetes and prediabetes and its risk factors in adults aged 25-64 in the Czech Republic: a cross-sectional study. *Diabetes Res Clin Pract*. (2020) 170:108470. doi: 10.1016/j.diabres.2020.108470

29. Hadi Alijanvand M, Aminorroaya A, Kazemi I, Amini M, Aminorroaya Yamini S, Mansourian M. Prevalence and predictors of prediabetes and its coexistence with high blood pressure in first-degree relatives of patients with type 2 diabetes: a 9-year cohort study. *J Res Med Sci*. (2020) 25:31. doi: 10.4103/jrms.JRMS_472_18

30. Matthews CE, Hebert JR, Freedson PS, Stanek EJ III, Merriam PA, Ebbeling CB, et al. Sources of variance in daily physical activity levels in the seasonal variation of blood cholesterol study. *Am J Epidemiol*. (2001) 153:987–95. doi: 10.1093/aje/153.10.987

31. Chen J, Luo Q, Su Y, Wang J, Fang Z, Luo F. Effects of physical activity on the levels of remnant cholesterol: a population-based study. *J Cell Mol Med*. 28:e18062. doi: 10.1111/jcmm.18062

32. Mann S, Beedie C, Jimenez A. Differential effects of aerobic exercise, resistance training and combined exercise modalities on cholesterol and the lipid profile: review, synthesis and recommendations. *Sports Med*. (2014) 44:211–21. doi: 10.1007/s40279-013-0110-5

33. Wei D, Marrachelli VG, Melgarejo JD, Liao CT, Janssens S, Verhamme P, et al. Lipoprotein profiles of fat distribution and its association with insulin sensitivity. *Front Endocrinol*. (2022) 13:978745. doi: 10.3389/fendo.2022.978745

34. Nakamura K, Miyoshi T, Yunoki K, Ito H. Postprandial hyperlipidemia as a potential residual risk factor. *J Cardiol*. (2016) 67:335–9. doi: 10.1016/j.jjcc.2015.12.001

35. Rasmussen L, Poulsen CW, Kampmann U, Smedegaard SB, Ovesen PG, Fuglsang J. Diet and healthy lifestyle in the management of gestational diabetes mellitus. *Nutrients*. (2020) 12:3050. doi: 10.3390/nu12103050

36. Haapala EA, Wiklund P, Lintu N, Tompuri T, Väistö J, Finni T, et al. Cardiorespiratory fitness, physical activity, and insulin resistance in children. *Med Sci Sports Exerc*. (2020) 52:1144–52. doi: 10.1249/MSS.0000000000002216

37. Lakka TA, Lintu N, Väistö J, Viitasalo A, Sallinen T, Haapala EA, et al. A 2 year physical activity and dietary intervention attenuates the increase in insulin resistance in a general population of children: the PANIC study. *Diabetologia*. (2020) 63:2270–81. doi: 10.1007/s00125-020-05250-0

38. Izumida T, Nakamura Y, Hino Y, Ishikawa S. Combined effect of small dense low-density lipoprotein cholesterol (sdLDL-C) and remnant-like particle cholesterol (RLP-C) on low-grade inflammation. *J Atheroscler Thromb*. (2020) 27:319–30. doi: 10.5551/jat.49528

39. Varbo A, Benn M, Tybjærg-Hansen A, Nordestgaard BG. Elevated remnant cholesterol causes both low-grade inflammation and ischemic heart disease, whereas elevated low-density lipoprotein cholesterol causes ischemic heart disease without inflammation. *Circulation*. (2013) 128:1298–309. doi: 10.1161/CIRCULATIONAHA.113.003008

40. El Assar M, Álvarez-Bustos A, Sosa P, Angulo J, Rodríguez-Mañas L. Effect of physical activity/exercise on oxidative stress and inflammation in muscle and vascular aging. *Int J Mol Sci*. (2022) 23:8713. doi: 10.3390/ijms23158713

41. Valenzuela PL, Ruilope LM, Santos-Lozano A, Wilhelm M, Kränkel N, Fiuza-Luces C, et al. Exercise benefits in cardiovascular diseases: from mechanisms to clinical implementation. *Eur Heart J*. (2023) 44:1874–89. doi: 10.1093/eurheartj/ehad170

42. Frodermann V, Rohde D, Courties G, Severe N, Schloss MJ, Amatullah H, et al. Exercise reduces inflammatory cell production and cardiovascular inflammation via instruction of hematopoietic progenitor cells. *Nat Med*. (2019) 25:1761–71. doi: 10.1038/s41591-019-0633-x

43. Zhang J, Chen Z, Pärna K, van Zon SKR, Snieder H, Thio CHL. Mediators of the association between educational attainment and type 2 diabetes mellitus: a two-step multivariable Mendelian randomisation study. *Diabetologia*. (2022) 65:1364–74. doi: 10.1007/s00125-022-05705-6

44. Geng T, Zhu K, Lu Q, Wan Z, Chen X, Liu L, et al. Healthy lifestyle behaviors, mediating biomarkers, and risk of microvascular complications among individuals with type 2 diabetes: a cohort study. *PLoS Med*. (2023) 20:e1004135. doi: 10.1371/journal.pmed.1004135

45. Aune D, Norat T, Leitzmann M, Tonstad S, Vatten LJ. Physical activity and the risk of type 2 diabetes: a systematic review and dose-response meta-analysis. *Eur J Epidemiol*. (2015) 30:529–42. doi: 10.1007/s10654-015-0056-z

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The effect of exercise on flow-mediated dilation in people with type 2 diabetes mellitus: a systematic review and meta-analysis of randomized controlled trials

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Introduction: An increasing number of studies have investigated the effect of exercise on flow-mediated dilation (FMD) in people with type 2 diabetes mellitus (T2DM), while the findings were controversial. The primary aim of this systematic review and meta-analysis was to investigate the effect of exercise on FMD in T2DM patients, and the secondary aim was to investigate the optimal type, frequency, session duration, and weekly time of exercise for T2DM patients.

Methods: Searches were conducted in PubMed, Cochrane Library, Scopus, Web of Science, Embase and EBSCO databases. The Cochrane risk of bias tool (RoB2) in randomized trial and Physiotherapy Evidence Database (PEDro) scale were used to assess the methodological quality of the included studies.

Results: From the 3636 search records initially retrieved, 13 studies met the inclusion criteria. Our meta-analysis revealed that exercise had a significant effect on improving FMD in T2DM patients [WMD, 2.18 (95% CI, 1.78-2.58), $p < 0.00001$, $I^2 = 38\%$], with high-intensity interval training (HIIT) being the most effective intervention type [HIIT, 2.62 (1.42-3.82); $p < 0.0001$; aerobic exercise, 2.20 (1.29-3.11), $p < 0.00001$; resistance exercise, 1.91 (0.01-3.82), $p = 0.05$; multicomponent training, 1.49 (0.15-2.83), $p = 0.03$]. In addition, a higher frequency [> 3 times, 3.06 (1.94-4.19), $p < 0.00001$; ≤ 3 times, 2.02 (1.59-2.45), $p < 0.00001$], a shorter session duration [< 60 min, 3.39 (2.07-4.71), $p < 0.00001$; ≥ 60 min, 1.86 (1.32-2.40), $p < 0.00001$], and a shorter weekly time [≤ 180 min, 2.40 (1.63-3.17), $p < 0.00001$; > 180 min, 2.11 (0.82-3.40), $p = 0.001$] were associated with larger improvements in FMD.

Conclusion: This meta-analysis provides clinicians with evidence to recommended that T2DM patients participate in exercise, especially HIIT, more than 3 times per week for less than 60 min, with a target of 180 min per week being reached by increasing the frequency of exercise.

Systematic review registration: https://www.crd.york.ac.uk/prospero, identifier CRD42023466575.

KEYWORDS

exercise, endothelial function, flow-mediated dilation, type 2 diabetes mellitus, systematic review, meta-analysis

1 Introduction

Type 2 diabetes mellitus (T2DM) is a prevalent chronic metabolic disease usually due to defective insulin secretion from pancreatic β-cells and a blunted insulin response in insulin-sensitive tissues (1). Patients with T2DM exhibit hyperglycemia, excessive release of free fatty acids (FFAs), insulin resistance, and hyperinsulinemia (2). Endothelial dysfunction, one of the pathological features of T2DM (3), is usually defined as decreased nitric oxide (NO) bioavailability (4), which may be triggered by elevated oxidative stress, leading to increased reactive oxidative substances (ROS), thereby impairing vascular endothelial function (4, 5). In addition, endothelial dysfunction and atherosclerosis are important factors affecting vascular complications in T2DM patients (6).

Endothelial dysfunction leads to a significantly increased risk of chronic diseases such as cardiovascular diseases (CVDs) and its associated complications (7, 8), which is a major cause of morbidity and mortality in T2DM patients (9). A previous study showed that T2DM patients had a doubled risk of developing CVDs (10). Flow-mediated dilation (FMD) is the non-invasive gold standard method for assessing arterial endothelial function (11, 12). Several studies have demonstrated that brachial artery FMD serves as an independent predictor of cardiovascular events (13–15). Therefore, it is important to develop programs to improve endothelial function for the prevention and treatment of T2DM and its associated chronic diseases (16).

Exercise, diet, and medication are important tools in the treatment of T2DM (17). However, exercise interventions are more cost-effective and convenient than other interventions. Studies have shown that exercise can improve the health of T2DM patients, including cardiovascular function (18–20), inflammation (21), cognitive function, and metabolic health (22). A meta-analysis showed that exercise had a significant effect on FMD in different populations (23). With the consensus on exercise as a treatment for T2DM (17), the potential benefits of exercise on FMD in T2DM patients have attracted considerable attention (24–36). However, the type of intervention can have a different impact on FMD in T2DM patients. Of these, aerobic exercise is the most studied type of exercise for T2DM and usually involves exercises that mobilize whole-body muscle groups, such as running, swimming, and brisk walking (37). In addition, traditional aerobic exercise tends to use lower intensity exercise, which means that a longer duration may be required to achieve the corresponding exercise effect. Unfortunately, obesity is a common complication of T2DM, with 80% of T2DM patients having obesity (38). Due to limited mobility and peripheral neuropathy (39), it may be difficult for these patients to ensure good compliance when performing prolonged whole-body exercise (40). In such cases, using resistance exercise that stimulates localized muscle groups or using shorter high-intensity interval training (HIIT) sessions may be a better option (24, 40). However, the effect of exercise and other modalities on the efficacy of FMD in T2DM patients remains unclear.

Therefore, the primary aim of this systematic review and meta-analysis was to investigate the effect of exercise on FMD in T2DM patients, and the secondary aim was to investigate the optimal type, frequency, session duration, and weekly time of exercise for T2DM patients. We hypothesized that exercise would significantly improve FMD in T2DM patients, with HIIT being the most effective type of intervention, and that the frequency and session duration would influence the efficacy of the exercise intervention, with the optimal combination being a higher frequency (more than 3 times per week) and a shorter session duration (less than 60 min).

2 Methods

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA, 2020) (41) and was registered on PROSPERO (CRD42023466575).

2.1 Search strategy

We searched the PubMed, Web of Science, Embase, EBSCO, Scopus, and Cochrane library for randomized controlled trials

(RCTs) relating to the effect of exercise on endothelial function in T2DM patients from the inception dates to 20 February, 2024 (Supplementary Table 1). Reference lists of relevant studies, including reviews and meta-analyses, were manually searched to identify additional relevant studies. The procedure was performed independently by two authors (BQ and YZ), and disagreement were resolved through discussion with the third author (LY).

2.2 Eligibility criteria

Inclusion criteria were: (1) RCTs; (2) using T2DM patients as subjects; (3) including an intervention and control groups; (4) using FMD as the outcome measure and the data were present as percentage.

Exclusion criteria were: (1) non-English articles; (2) conference abstracts; (3) animal studies; (4) reviews.

2.3 Data extraction

The data extraction was conducted by two authors (BQ and YZ), including: (1) surname of the first author, publication year, and sample size; (2) categorized variable: intervention type [aerobic exercise, HIIT, resistance exercise, and multicomponent training (a training modality that involves different physical capacities in the same exercise session) (42)] and continuous variables: duration, session duration, frequency, and weekly time; (3) participants' age and disease duration; and (4) mean and standard deviation (SD) values reflecting changes in FMD, as described previously (43).

2.4 Methodological quality assessment

The version 2 of the Cochrane risk of bias tool (RoB2) in randomized trial and Physiotherapy Evidence Database (PEDro) scale were used to assess the methodological quality of included studies (44, 45). RoB2 was assessed mainly from 7 items: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other biases. For PEDro scale, 11 items were evaluated, where studies scoring < 4 points, 4-5 points, 6-8 points, and > 9 points are considered poor, average, good, and excellent quality, respectively (46).

2.5 Statistical analysis

Weighted mean differences (WMDs) and 95% confidence intervals (CIs) were used to estimate the effects of exercise on FMD in T2DM patients. For included studies reporting standard error (SE) or 95% CI, SD was calculated using the previously described formula (47). Heterogeneity was assessed using the I^2 static, where I^2 < 25% indicate no significant heterogeneity, 25% < I^2 < 50% indicate low heterogeneity, 50% < I^2 < 75% indicate moderate heterogeneity, and I^2 > 75% indicate high heterogeneity (48). Data were pooled using fixed effects models or random effects models when I^2 < 50% or I^2 ≥ 50%, respectively (49). Subgroup analysis, meta-regression analysis, and sensitivity analysis were used to interpret the results if there was a high heterogeneity (I^2 > 60%) (43).

For subgroup analyses, we examined the effect of intervention type (aerobic exercise, HIIT, resistance exercise, and multicomponent exercise), frequency (≤ 3 times and > 3 times), session duration (< 60 min and ≥ 60 min), and weekly time (≤ 180 min and > 180 min) on FMD in T2DM patients. Meta-regressions were conducted based on the participants' age, disease duration, frequency, session duration, and weekly time. The forest plots were generated using Review manager software (Version 5.4; Cochrane Collaboration), and sensitivity analysis, meta-regressions, and funnel plot were performed using Stata software (Version 15.0, Stata Corp, College Station, Texas). Statistical significance was considered for outcomes with a $p < 0.05$.

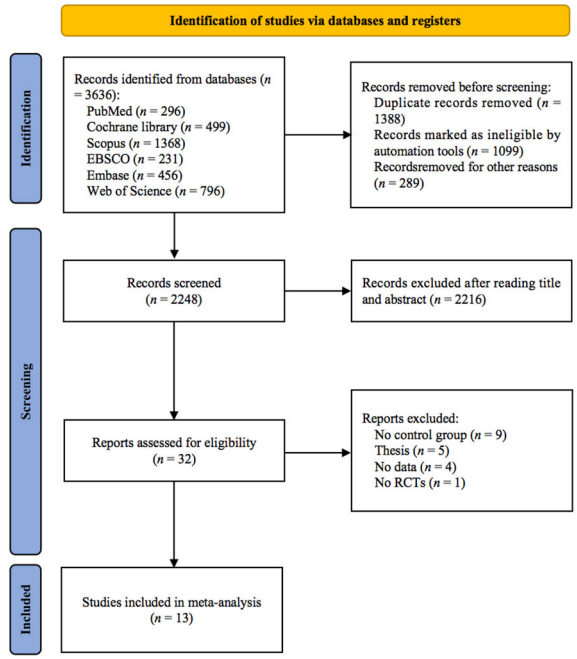

FIGURE 1
PRISMA flowchart of study selection.

3 Results

3.1 Study selection

As shown in Figure 1, 3636 studies were identified from 6 databases. After excluding duplicates, 2248 studies remained, and after screening titles and abstracts, 32 studies remained. Nineteen studies were excluded for the following reasons: (1) no control group (n = 9); (2) thesis (n = 5); (3) no data (n = 4); and (4) no RCTs (n = 1). Finally, 13 studies (24–36) met the inclusion criteria.

3.2 Study characteristics

As shown in Supplementary Table 2, among the included studies, there were 290 T2DM patients in the 18 intervention groups and 233 T2DM patients in the 13 control groups. Among the included studies, 3 studies (24, 30, 34) involved only women, 1 study (29) involved only men, and 9 studies (25–28, 31–35) involved both men and women. The mean age of the participants ranged from 15.3 to 70.5 years. The mean age of participants in 2 studies (24, 32) was < 45 years, and 11 studies (25–31, 33–36) involved participants with mean age ≥ 45 years. The mean time from T2DM to intervention of participants ranged from 1.43 to 21.1 years. Most interventions specified aerobic exercise (n = 7) (26, 28–31, 34, 35), high-intensity interval training (HIIT, n = 5) (24, 26–28, 31), resistance exercise (n = 3) (27, 30, 36), and multicomponent training (n = 3) (25, 32, 33). For aerobic exercise, the total duration of intervention ranged from 8 to 12 weeks, with an average of 11.3 weeks, the frequency of intervention per week was 3 times, and minutes of intervention per session ranged from 30 to 62 minutes, with an average of 54 minutes. For HIIT, the total duration of intervention was 12 weeks, the frequency of intervention per week was 3 times, the number of intervals ranged from 3 to 11 times, with an average of 7 times, the interval time ranged from 1 to 3 minutes, with an average of 2 minutes, and the number of repetitions per session ranged from 4 to 12 times, with an average of 8 times. For resistance exercise, the total duration of intervention was 12 weeks and the frequency of intervention per week was 3 times. For multicomponent training, the total duration of intervention ranged from 12 to 24 weeks, with an average of 16 weeks, the frequency of intervention per week ranged from 3 to 5 times, and minutes of intervention per session ranged from 60 to 75 minutes, with an average of 67.5 minutes. The session duration ranged from 19 to 75 min, while 1 study (36) did not provide information on session duration. The frequency ranged from 3 to 5 times per week, and we calculated the weekly time based on frequency and session duration (42), which ranged from 90 to 300 min. The results of FMD in all included studies were presented as percentages.

3.3 Risk of bias

The RoB2 was used to assess the quality of the included studies in terms of selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias (Figure 2). The PEDro scale showed that of the 13 included studies, 1 were of excellent quality and 12 was of good quality (Supplementary Table 3).

3.4 Meta-analysis results

3.4.1 Effects of exercise on FMD in T2DM patients

Exercise had a significant effect on improving FMD in T2DM patients [WMD, 2.18 (95% CI, 1.78-2.58); p < 0.00001; I^2 = 38%; Figure 3].

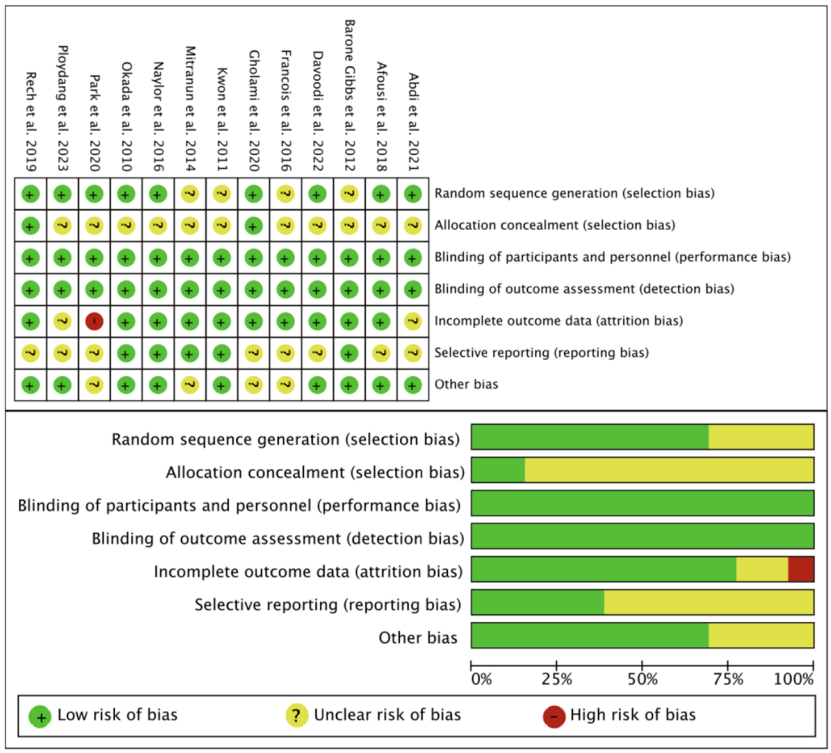

FIGURE 2
Results of Cochrane risk of bias tool.

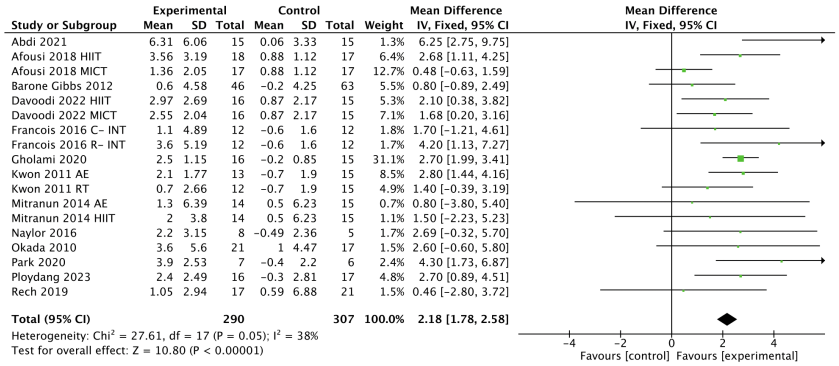

FIGURE 3
Meta-analysis results of the effect of exercise on FMD in T2DM patients.

3.4.2 Subgroup analysis

As shown in Figure 4, subgroup analysis showed that HIIT [WMD, 2.62 (95% CI, 1.42-3.82; $p < 0.0001$; $I^2 = 23\%$], aerobic exercise [WMD, 2.20 (95% CI, 1.29-3.11); $p < 0.00001$; $I^2 = 61\%$], resistance exercise [WMD, 1.91 (95% CI, 0.01-3.82); $p = 0.05$; $I^2 = 37\%$], and multicomponent training [WMD, 1.49 (95% CI, 0.15-2.83); $p = 0.03$; $I^2 = 0\%$] were effective in improving FMD in T2DM patients, with HIIT being the most effective intervention type.

In addition, subgroup analyses indicated that a higher frequency [> 3 times, WMD, 3.06 (95% CI, 1.94-4.19); $p < 0.00001$; $I^2 = 0\%$; ≤ 3 times, WMD, 2.02 (95% CI, 1.59-2.45); $p < 0.00001$; $I^2 = 45\%$; Figure 5], a shorter session duration [< 60 min, WMD, 3.39 (95% CI, 2.07-4.71); $p < 0.00001$; $I^2 = 27\%$; ≥ 60 min, WMD, 1.86 (95% CI, 1.32-2.40); $p < 0.00001$; $I^2 = 24\%$; Figure 6], and a shorter weekly time (≤ 180 min, WMD, 2.40 [95% CI, 1.63-3.17); $p < 0.00001$; $I^2 = 0\%$; > 180 min, WMD, 2.11 (95% CI, 0.82-3.40); $p = 0.001$; $I^2 = 65\%$; Figure 7] were associated with larger improvements in FMD.

3.5 Meta regression

Meta-regression analyses were performed on intervention duration, session duration, frequency, weekly time, participants' age, and disease duration. No significant associations were observed between intervention duration ($p = 0.128$, Supplementary Figure 1), frequency ($p = 0.144$, Supplementary Figure 2), weekly time ($p = 0.636$, Supplementary Figure 3), session duration ($p = 0.297$, Supplementary Figure 4), age ($p = 0.213$, Supplementary Figure 5), or disease duration ($p = 0.569$, Supplementary Figure 6) and FMD.

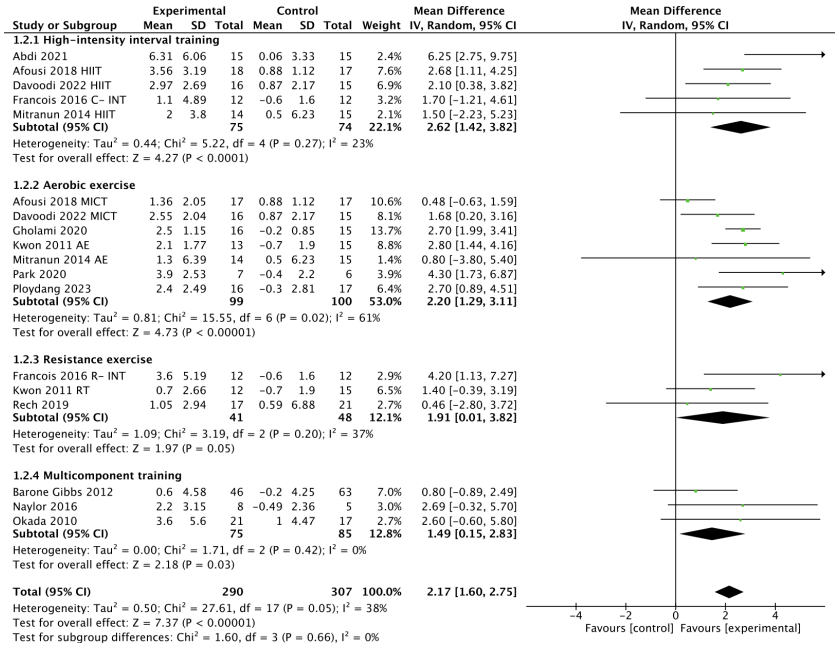

FIGURE 4
Meta-analysis results of the effect of different types of intervention on FMD in T2DM patients.

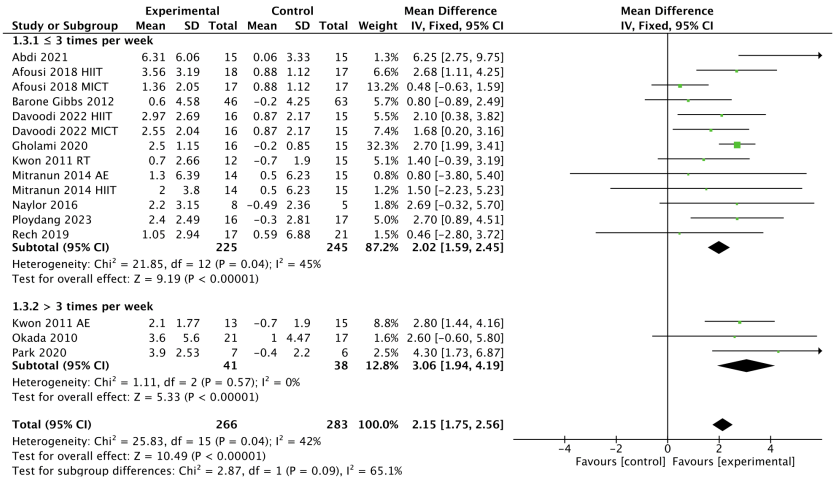

FIGURE 5
Meta-analysis results of the effect of the frequency of intervention on FMD in T2DM patients.

3.6 Publication bias

Possible publication bias was evaluated by the funnel plot (Figure 8). Visual inspection of the funnel plot suggested the absence of funnel plot asymmetry. Based on the results of egger's test, small sample size studies were insufficient to affect the final results (p = 0.775, Supplementary Table 4).

3.7 Sensitivity analysis

Sensitivity analysis showed that there is no change in the direction or level of compatibility of the overall effect of exercise on FMD in T2DM patients when any of the included studies are omitted (Supplementary Figure 7).

4 Discussion

4.1 Effects of exercise on FMD in T2DM patients

In this study, we aimed to investigate the effect of exercise on FMD in T2DM patients and the optimal type, frequency, session duration, and weekly time of exercise for T2DM patients, and a total of 13 studies containing data from 523 patients were included. Our results showed that exercise significantly improved FMD in T2DM patients, which was consistent with the results of previous studies (50–52). In terms of WMD, exercise improved FMD by 2.18% in T2DM patients, which has significant clinical implications for individuals with T2DM. A previous meta-analysis showed that for every 1% increase in FMD, the risk of cardiovascular events was

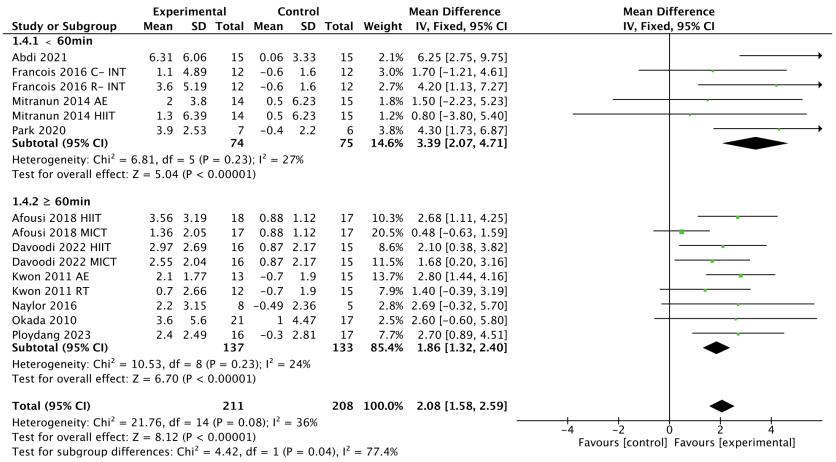

FIGURE 6
Meta-analysis results of the effect of the duration of intervention per session on FMD in T2DM patients.

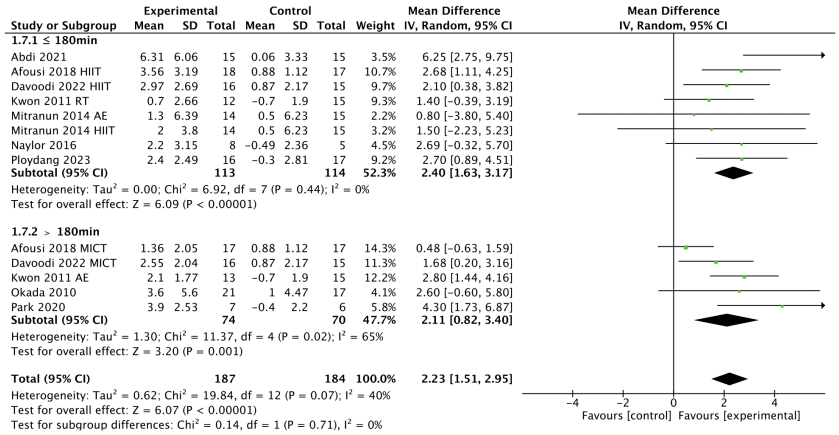

FIGURE 7
Meta-analysis results of the effect of the duration of intervention per week on FMD in T2DM patients.

expected to decreased by 13% (53). Meanwhile, we noted the inclusion of studies combining exercise and dietary interventions in previous meta-analyses (50, 51), which may be due to the limited number of studies on the effect of exercise interventions alone on endothelial function in T2DM patients. Notably, our meta-analysis avoided this limitation by excluding studies combining exercise and dietary interventions (54–56), and none of the 13 included studies involved dietary interventions. This is because dietary interventions may have a confounding effect with exercise, thus masking the true efficacy of exercise in T2DM patients (57, 58).

Although the exact mechanisms remain incompletely elucidated, it can be hypothesized that the benefits of exercise on endothelial function can be amplified through the following mechanisms. First of all, shear stress plays a central role in regulating the inflammatory response of the vascular endothelium and the pathogenesis of atherosclerosis (59). Several studies have shown that exercise leads to an increase in blood flow, which in turn increases the shear stress of blood flow (60, 61), suggesting that the vascular endothelium is induced to synthesize more NO synthesis and increase the bioavailability of NO (62, 63). Secondly, both oxidative stress and inflammation are among the risk factors for vascular endothelial diseases (64, 65), and both are initiating factors for endothelial dysfunction. However, exercise has been shown to have anti-inflammatory properties and to reduce oxidative stress as a non-pharmacological intervention (66, 67). On the one hand, exercise reduces low-grade inflammation biomarkers and endothelial dysfunction biomarkers in plasma (68). In addition, exercise also affects oxidative stress by increasing the availability of antioxidant enzymes, thus improving endothelial function (62, 69). Furthermore, endothelial progenitor cells (EPCs) may also server as biomarkers of cardiovascular function (70), and Ribeiro et al. (71) showed that exercise increased the number and differentiation capacity of EPCs, which may contribute to vascular regeneration and angiogenesis. Thus, an increased in the number of EPCs may positively affect endothelial function (72, 73).

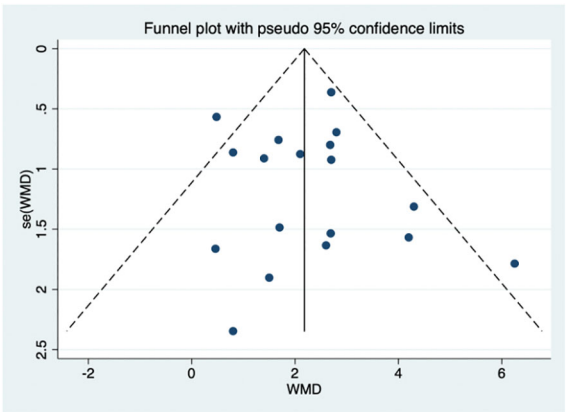

FIGURE 8
Funnel plot.

4.2 Subgroup analysis

Subgroup analysis of different types of intervention showed that HIIT, aerobic exercise, resistance exercise, and multi-component training were all effective in improving FMD in T2DM patients, with HIIT being the most effective intervention type, although aerobic exercise is widely used to improve chronic disease. This may be due to the fact that intensity is an important factor in FMD (28), and HIIT tends to be higher in intensity compared to aerobic exercise or other interventions. Thijssen et al. (74) showed that vascular blood flow and shear stress improved with increasing exercise intensity. Elevated vascular shear stress due to HIIT would lead to potassium channel activation and increased Ca^{2+} entering the vascular endothelium. Elevated intracellular Ca^{2+} concentration triggers activation of endothelial nitric oxide synthase (eNOS) (75, 76). In addition, HIIT may also lead to decreased catecholamine levels and α-adrenoceptor density (77, 78). Furthermore, adropin, as a regulator of eNOS synthase and NO release, has been implicated as a potential factor affecting

endothelial function. A previous study showed that elevated adropin levels increased eNOS mRNA expression (79), indicating that elevated adropin may contribute to the reduction of exercise-induced atherosclerosis (80). Thus, elevated adropin may be considered a marker of improved endothelial function (24). Although the mechanism by which exercise leads to elevated adropin levels is unknown, it was observed in one study that a 12-week HIIT intervention significantly increased adropin levels in T2DM patients (24). Meanwhile, in another clinical trial using HIIT and MICT as interventions, a greater increase in adropin was observed in the HIIT group than in the MICT group (26). Moreover, a recent study (73) has shown that HIIT is superior to MICT in mobilizing circulating EPCs. All of these mechanisms appear to lead to greater NO production and increased NO bioavailability, thus well explaining the further improvement in FMD. Moreover, our result was consistent with a meta-analysis conducted by Ramos et al. (81), showing that HIIT was more effective in improving FMD compared to MICT.

Regarding intervention frequency, our subgroup analysis showed that interventions performed more than 3 times per week had a greater improvement in FMD compared to interventions performed up to 3 times per week, which was in agreement with a previous study (30), showing that high-frequency interventions are more beneficial than low-frequency interventions for endothelial function in T2DM patients. This hypothesis is also supported by a meta-analysis conducted by Fuertes-Kenneally et al. (82), showing that a higher frequency of intervention per week was associated with a better effect on endothelial function improvement. However, we believe that the frequency of intervention may be influenced by other factors, such as session duration and weekly time.

It is reported that the effects of exercise on health have a dose-response relationship, and that it is not more exercise that is beneficial, but rather the appropriate load that determines the health benefits of exercise (83). Several studies have found that engaging in extraordinarily prolonged exercise does not seem to provide corresponding benefits to the body and can even trigger negative effects on cardiac function (84–86). The benefits of exercise on endothelial function seem to apply here as well. Our subgroup analysis showed greater improvements in FMD in T2DM patients with exercise conducted less than 60 min compared to 60 min or more per session. It has been shown that T2DM patients typically have lower exercise tolerance (39), which may make it difficult for them to perform prolonged exercise during each session. Therefore, it can be concluded that a longer exercise duration does not contribute to more improvement in T2DM patients, and that a single session of less than 60 min may be more favorable for adherence to exercise and associated health benefits in T2DM patients.

However, our previous study found that the use of frequency and session duration alone did not exclude the influence of other variables (49). Therefore, we considered introducing weekly time to provide new ideas for exercise prescription. The weekly time was calculated based on the frequency and session duration. The World Health Organization (WHO) recommends that people perform 150-300 min of moderate-intensity aerobic exercise, 75-150 minutes of vigorous-intensity aerobic exercise, or an equal combination of moderate- and vigorous-intensity each week (87). Our subgroup analysis showed that a shorter weekly time (≤ 180 min *vs.* > 180 min) were associated with a larger improvement in FMD, which may also be related to the exercise tolerance of T2DM patients, for which more than 180 min per week does not seem to provide additional physical benefits.

4.3 Strengths and limitations of this systematic review

In this systematic review and meta-analysis, we included studies on the effect of exercise interventions alone on FMD in T2DM patients, and excluded studies where exercise was combined with dietary interventions, which can better reflect the effect of exercise interventions. Our findings provide an optimal combination of exercise modalities for T2DM patients. Clinically, T2DM patients can improve endothelial function by engaging in exercise 3 times per week for less than 60 min each time, especially HIIT, to achieve the goal of 180 min of exercise per week.

However, the present study has some limitations that should be noted. Although previous studies have found that improvement in FMD in T2DM patients decreases as the duration of intervention increases, it was not possible to investigate the effect of duration on the degree of improvement in FMD because the duration of the interventions in the included studies was generally focused on 12 weeks. In addition, although our study found that HIIT is the most effective intervention type for improving FMD in T2DM patients. However, due to the limited number of studies using HIIT in T2DM patients, we were unable to examine the optimal design of HIIT interventions. Finally, the studies we included contained aerobic exercise, HIIT, resistance exercise, and multicomponent exercise, and we were unable to standardize the intensity of exercise, so we were unable to explore the effect of intensity on FMD in T2DM patients.

5 Conclusion

In this meta-analysis, exercise had beneficial effect in improving FMD in T2DM patients, with HIIT being the most effective intervention type. To improve endothelial function, this meta-analysis provides clinicians with evidence to recommended that T2DM patients participate in exercise, especially HIIT, more than 3 times per week for less than 60 min, with a target of 180 min per week being reached by increasing the frequency of exercise.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Author contributions

BQ: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. YZ: Data curation, Formal analysis, Investigation, Methodology, Software, Validation, Visualization, Writing – original draft. XT: Data curation, Formal analysis, Writing – review & editing. XH: Data curation, Formal analysis, Writing – review & editing. LD: Data curation, Formal analysis, Writing – review & editing. YL: Data curation, Formal analysis, Writing – review & editing. LY: Conceptualization, Data curation, Funding acquisition, Methodology, Project administration, Resources, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2024.1347399/full#supplementary-material

References

1. Roden M, Shulman GI. The integrative biology of type 2 diabetes. *Nature*. (2019) 576:51–60. doi: 10.1038/s41586-019-1797-8

2. Zhang H, Dellsperger KC, Zhang C. The link between metabolic abnormalities and endothelial dysfunction in type 2 diabetes: an update. *Basic Res Cardiol*. (2012) 107:237. doi: 10.1007/s00395-011-0237-1

3. Avogaro A, Albiero M, Menegazzo L, de Kreutzenberg S, Fadini GP. Endothelial dysfunction in diabetes: the role of reparatory mechanisms. *Diabetes Care*. (2011) 34 Suppl 2:S285–90. doi: 10.2337/dc11-s239

4. Jansson PA. Endothelial dysfunction in insulin resistance and type 2 diabetes. *J Intern Med*. (2007) 262:173–83. doi: 10.1111/j.1365-2796.2007.01830.x

5. Xu S, Ilyas I, Little PJ, Li H, Kamato D, Zheng X, et al. Endothelial dysfunction in atherosclerotic cardiovascular diseases and beyond: from mechanism to pharmacotherapies. *Pharmacol Rev*. (2021) 73:924–67. doi: 10.1124/pharmrev.120.000096

6. Woodman RJ, Chew GT, Watts GF. Mechanisms, significance and treatment of vascular dysfunction in type 2 diabetes mellitus: focus on lipid-regulating therapy. *Drugs*. (2005) 65:31–74. doi: 10.2165/00003495-200565010-00003

7. De Vriese AS, Verbeuren TJ, Van de Voorde J, Lameire NH, Vanhoutte PM. Endothelial dysfunction in diabetes. *Br J Pharmacol*. (2000) 130:963–74. doi: 10.1038/sj.bjp.0703393

8. Nakagawa T, Tanabe K, Croker BP, Johnson RJ, Grant MB, Kosugi T, et al. Endothelial dysfunction as a potential contributor in diabetic nephropathy. *Nat Rev Nephrol*. (2011) 7:36–44. doi: 10.1038/nrneph.2010.152

9. Robson R, Kundur AR, Singh I. Oxidative stress biomarkers in type 2 diabetes mellitus for assessment of cardiovascular disease risk. *Diabetes Metab Syndr*. (2018) 12:455–62. doi: 10.1016/j.dsx.2017.12.029

10. Sarwar N, Gao P, Seshasai SR, Gobin R, Kaptoge S, Di Angelantonio E, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: A collaborative meta-analysis of 102 prospective studies. *Lancet*. (2010) 375:2215–22. doi: 10.1016/s0140-6736(10)60484-9

11. Anderson EA, Mark AL. Flow-mediated and reflex changes in large peripheral artery tone in humans. *Circulation*. (1989) 79:93–100. doi: 10.1161/01.cir.79.1.93

12. Deanfield JE, Halcox JP, Rabelink TJ. Endothelial function and dysfunction: testing and clinical relevance. *Circulation*. (2007) 115:1285–95. doi: 10.1161/circulationaha.106.652859

13. Yeboah J, Folsom AR, Burke GL, Johnson C, Polak JF, Post W, et al. Predictive value of brachial flow-mediated dilation for incident cardiovascular events in a population-based study: the multi-ethnic study of atherosclerosis. *Circulation*. (2009) 120:502–9. doi: 10.1161/circulationaha.109.864801

14. Thijssen DHJ, Bruno RM, van Mil A, Holder SM, Faita F, Greyling A, et al. Expert consensus and evidence-based recommendations for the assessment of flow-mediated dilation in humans. *Eur Heart J*. (2019) 40:2534–47. doi: 10.1093/eurheartj/ehz350

15. Shechter M, Issachar A, Marai I, Koren-Morag N, Freinark D, Shahar Y, et al. Long-term association of brachial artery flow-mediated vasodilation and cardiovascular events in middle-aged subjects with no apparent heart disease. *Int J Cardiol*. (2009) 134:52–8. doi: 10.1016/j.ijcard.2008.01.021

16. Avogaro A, de Kreutzenberg SV, Fadini G. Endothelial dysfunction: causes and consequences in patients with diabetes mellitus. *Diabetes Res Clin Pract*. (2008) 82:S94–s101. doi: 10.1016/j.diabres.2008.09.021

17. Sigal RJ, Kenny GP, Wasserman DH, Castaneda-Sceppa C, White RD. Physical activity/exercise and type 2 diabetes: A consensus statement from the American diabetes association. *Diabetes Care*. (2006) 29:1433–8. doi: 10.2337/dc06-9910

18. Qiu Y, Fernández-García B, Lehmann HI, Li G, Kroemer G, López-Otín C, et al. Exercise sustains the hallmarks of health. *J Sport Health Sci*. (2023) 12:8–35. doi: 10.1016/j.jshs.2022.10.003

19. Fine J. Exercise and fitness. *Jama*. (1964) 188:433–6. doi: 10.1001/jama.1964.03060310033007

20. Chen H, Chen C, Spanos M, Li G, Lu R, Bei Y, et al. Exercise training maintains cardiovascular health: signaling pathways involved and potential therapeutics. *Signal Transduct Target Ther*. (2022) 7:306. doi: 10.1038/s41392-022-01153-1

21. Magalhães JP, Santos DA, Correia IR, Hetherington-Rauth M, Ribeiro R, Raposo JF, et al. Impact of combined training with different exercise intensities on inflammatory and lipid markers in type 2 diabetes: A secondary analysis from a 1-year randomized controlled trial. *Cardiovasc Diabetol*. (2020) 19:169. doi: 10.1186/s12933-020-01136-y

22. Zhang J, Tam WWS, Kanokwan H, Kusuyama J, Wu VX. Effectiveness of combined aerobic and resistance exercise on cognition, metabolic health, physical function, and health-related quality of life in middle-aged and older adults with type 2 diabetes mellitus: A systematic review and meta-analysis. *Arch Phys Med Rehabil*. (2023) 000:1–15. doi: 10.1016/j.apmr.2023.10.005

23. Ashor AW, Lara J, Siervo M, Celis-Morales C, Oggioni C, Jakovljevic DG, et al. Exercise modalities and endothelial function: A systematic review and dose-response meta-analysis of randomized controlled trials. *Sports Med*. (2015) 45:279–96. doi: 10.1007/s40279-014-0272-9

24. Abdi S, Tadibi V, Sheikholeslami-Vatani D. Effect of high-intensity interval training on endothelial function in type 2 diabetic females. *Asian J Sports Med*. (2021) 12:e113566. doi: 10.5812/asjsm.113566

25. Barone Gibbs B, Dobrosielski DA, Bonekamp S, Stewart KJ, Clark JM. A randomized trial of exercise for blood pressure reduction in type 2 diabetes: effect on flow-mediated dilation and circulating biomarkers of endothelial function. *Atherosclerosis*. (2012) 224:446–53. doi: 10.1016/j.atherosclerosis.2012.07.035

26. Davoodi M, Hesamabadi BK, Ariabood E, Izadi MR, Ghardashi-Afousi A, Bigi MAB, et al. Improved blood pressure and flow-mediated dilatation via increased plasma adropin and nitrate/nitrite induced by high-intensity interval training in patients with type 2 diabetes. *Exp Physiol*. (2022) 107:813–24. doi: 10.1113/ep089371

27. Francois ME, Durrer C, Pistawka KJ, Halperin FA, Little JP. Resistance-based interval exercise acutely improves endothelial function in type 2 diabetes. *Am J Physiol Heart Circ Physiol*. (2016) 311:H1258–h67. doi: 10.1152/ajpheart.00398.2016

28. Ghardashi Afousi A, Izadi MR, Rakhshan K, Mafi F, Biglari S, Gandomkar Bagheri H. Improved brachial artery shear patterns and increased flow-mediated dilatation after low-volume high-intensity interval training in type 2 diabetes. *Exp Physiol*. (2018) 103:1264–76. doi: 10.1113/ep087005

29. Gholami F, Nazari H, Alimi M. Cycle training improves vascular function and neuropathic symptoms in patients with type 2 diabetes and peripheral neuropathy: A randomized controlled trial. *Exp Gerontol*. (2020) 131:110799. doi: 10.1016/j.exger.2019.110799

30. Kwon HR, Min KW, Ahn HJ, Seok HG, Lee JH, Park GS, et al. Effects of aerobic exercise vs. Resistance training on endothelial function in women with type 2 diabetes mellitus. *Diabetes Metab J*. (2011) 35:364–73. doi: 10.4093/dmj.2011.35.4.364

31. Mitranun W, Deerochanawong C, Tanaka H, Suksom D. Continuous vs interval training on glycemic control and macro- and microvascular reactivity in type 2 diabetic patients. *Scand J Med Sci Sports*. (2014) 24:e69–76. doi: 10.1111/sms.12112

32. Naylor LH, Davis EA, Kalic RJ, Paramalingam N, Abraham MB, Jones TW, et al. Exercise training improves vascular function in adolescents with type 2 diabetes. *Physiol Rep*. (2016) 4:e12713. doi: 10.14814/phy2.12713

33. Okada S, Hiuge A, Makino H, Nagumo A, Takaki H, Konishi H, et al. Effect of exercise intervention on endothelial function and incidence of cardiovascular disease in patients with type 2 diabetes. *J Atheroscler Thromb*. (2010) 17:828–33. doi: 10.5551/jat.3798

34. Park LK, Parks EJ, Pettit-Mee RJ, Woodford ML, Ghiarone T, Smith JA, et al. Skeletal muscle microvascular insulin resistance in type 2 diabetes is not improved by eight weeks of regular walking. *J Appl Physiol (1985)*. (2020) 129:283–96. doi: 10.1152/japplphysiol.00174.2020

35. Ploydang T, Khovidhunkit W, Tanaka H, Suksom D. Nordic walking in water on cerebrovascular reactivity and cognitive function in elderly patients with type 2 diabetes. *Med Sci Sports Exerc*. (2023) 55:1803–11. doi: 10.1249/mss.0000000000003216

36. Rech A, Botton CE, Lopez P, Quincozes-Santos A, Umpierre D, Pinto RS. Effects of short-term resistance training on endothelial function and inflammation markers in elderly patients with type 2 diabetes: A randomized controlled trial. *Exp Gerontol*. (2019) 118:19–25. doi: 10.1016/j.exger.2019.01.003

37. Boulé NG, Haddad E, Kenny GP, Wells GA, Sigal RJ. Effects of exercise on glycemic control and body mass in type 2 diabetes mellitus: A meta-analysis of controlled clinical trials. *Jama*. (2001) 286:1218–27. doi: 10.1001/jama.286.10.1218

38. Bloomgarden ZT. American diabetes association annual meeting, 1999: diabetes and obesity. *Diabetes Care*. (2000) 23:118–24. doi: 10.2337/diacare.23.1.118

39. Yang Z, Scott CA, Mao C, Tang J, Farmer AJ. Resistance exercise versus aerobic exercise for type 2 diabetes: A systematic review and meta-analysis. *Sports Med*. (2014) 44:487–99. doi: 10.1007/s40279-013-0128-8

40. Praet SF, van Loon LJ. Optimizing the therapeutic benefits of exercise in type 2 diabetes. *J Appl Physiol (1985)*. (2007) 103:1113–20. doi: 10.1152/japplphysiol.00566.2007

41. 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

42. Li G, You Q, Hou X, Zhang S, Du L, Lv Y, et al. The effect of exercise on cognitive function in people with multiple sclerosis: A systematic review and meta-analysis of randomized controlled trials. *J Neurol*. (2023) 270:2908–23. doi: 10.1007/s00415-023-11649-7

43. Tao X, Chen Y, Zhen K, Ren S, Lv Y, Yu L. Effect of continuous aerobic exercise on endothelial function: A systematic review and meta-analysis of randomized controlled trials. *Front Physiol*. (2023) 14:1043108. doi: 10.3389/fphys.2023.1043108

44. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane collaboration's tool for assessing risk of bias in randomised trials. *Bmj*. (2011) 343:d5928. doi: 10.1136/bmj.d5928

45. Zhen K, Zhang S, Tao X, Li G, Lv Y, Yu L. A systematic review and meta-analysis on effects of aerobic exercise in people with Parkinson's disease. *NPJ Parkinsons Dis*. (2022) 8:146. doi: 10.1038/s41531-022-00418-4

46. Zhang S, Zhen K, Su Q, Chen Y, Lv Y, Yu L. The effect of aerobic exercise on cognitive function in people with Alzheimer's disease: A systematic review and meta-analysis of randomized controlled trials. *Int J Environ Res Public Health*. (2022) 19:15700. doi: 10.3390/ijerph192315700

47. You Q, Yu L, Li G, He H, Lv Y. Effects of different intensities and durations of aerobic exercise on vascular endothelial function in middle-aged and elderly people: A meta-analysis. *Front Physiol*. (2021) 12:803102. doi: 10.3389/fphys.2021.803102

48. Wang Z, Qiu B, Gao J, Del Coso J. Effects of caffeine intake on endurance running performance and time to exhaustion: A systematic review and meta-analysis. *Nutrients*. (2022) 15:148. doi: 10.3390/nu15010148

49. Li G, Lv Y, Su Q, You Q, Yu L. The effect of aerobic exercise on pulse wave velocity in middle-aged and elderly people: A systematic review and meta-analysis of randomized controlled trials. *Front Cardiovasc Med*. (2022) 9:960096. doi: 10.3389/fcvm.2022.960096

50. Montero D, Walther G, Benamo E, Perez-Martin A, Vinet A. Effects of exercise training on arterial function in type 2 diabetes mellitus: A systematic review and meta-analysis. *Sports Med*. (2013) 43:1191–9. doi: 10.1007/s40279-013-0085-2

51. Qiu S, Cai X, Yin H, Sun Z, Zügel M, Steinacker JM, et al. Exercise training and endothelial function in patients with type 2 diabetes: A meta-analysis. *Cardiovasc Diabetol*. (2018) 17:64. doi: 10.1186/s12933-018-0711-2

52. Lee J-H, Lee R, Hwang M-H, Hamilton MT, Park Y. The effects of exercise on vascular endothelial function in type 2 diabetes: A systematic review and meta-analysis. *Diabetol Metab Syndrome*. (2018) 10:15. doi: 10.1186/s13098-018-0316-7

53. Inaba Y, Chen JA, Bergmann SR. Prediction of future cardiovascular outcomes by flow-mediated vasodilatation of brachial artery: A meta-analysis. *Int J Cardiovasc Imaging*. (2010) 26:631–40. doi: 10.1007/s10554-010-9616-1

54. Wycherley TP, Brinkworth GD, Noakes M, Buckley JD, Clifton PM. Effect of caloric restriction with and without exercise training on oxidative stress and endothelial function in obese subjects with type 2 diabetes. *Diabetes Obes Metab*. (2008) 10:1062–73. doi: 10.1111/j.1463-1326.2008.00863.x

55. Yezhova O, Melekhovets O, Olha S, Kovalenko Y, Ol'khovyk A, Melekhovets Y, et al. Impact of the multimodal physical program on the endothelium function in diabetic patients with obesity. *Acta Balneologica*. (2019) 61:11–6. doi: 10.36740/ABal201901102

56. Leehey DJ, Collins E, Kramer HJ, Cooper C, Butler J, McBurney C, et al. Structured exercise in obese diabetic patients with chronic kidney disease: A randomized controlled trial. *Am J Nephrol*. (2016) 44:54–62. doi: 10.1159/000447703

57. Hamdy O, Ledbury S, Mullooly C, Jarema C, Porter S, Ovalle K, et al. Lifestyle modification improves endothelial function in obese subjects with the insulin resistance syndrome. *Diabetes Care*. (2003) 26:2119–25. doi: 10.2337/diacare.26.7.2119

58. Schwingshackl L, Hoffmann G. Mediterranean dietary pattern, inflammation and endothelial function: A systematic review and meta-analysis of intervention trials. *Nutr Metab Cardiovasc Dis*. (2014) 24:929–39. doi: 10.1016/j.numecd.2014.03.003

59. Zakkar M, Angelini GD, Emanueli C. Regulation of vascular endothelium inflammatory signalling by shear stress. *Curr Vasc Pharmacol*. (2016) 14:181–6. doi: 10.2174/1570161114666151202205139

60. Goto C, Higashi Y, Kimura M, Noma K, Hara K, Nakagawa K, et al. Effect of different intensities of exercise on endothelium-dependent vasodilation in humans: role of endothelium-dependent nitric oxide and oxidative stress. *Circulation*. (2003) 108:530–5. doi: 10.1161/01.Cir.0000080893.55729.28

61. Niebauer J, Cooke JP. Cardiovascular effects of exercise: role of endothelial shear stress. *J Am Coll Cardiol*. (1996) 28:1652–60. doi: 10.1016/s0735-1097(96)00393-2

62. Di Francescomarino S, Sciartilli A, Di Valerio V, Di Baldassarre A, Gallina S. The effect of physical exercise on endothelial function. *Sports Med*. (2009) 39:797–812. doi: 10.2165/11317750-000000000-00000

63. Taddei S, Galetta F, Virdis A, Ghiadoni L, Salvetti G, Franzoni F, et al. Physical activity prevents age-related impairment in nitric oxide availability in elderly athletes. *Circulation*. (2000) 101:2896–901. doi: 10.1161/01.cir.101.25.2896

64. Steven S, Frenis K, Oelze M, Kalinovic S, Kuntic M, Bayo Jimenez MT, et al. Vascular inflammation and oxidative stress: major triggers for cardiovascular disease. *Oxid Med Cell Longev*. (2019) 2019:7092151. doi: 10.1155/2019/7092151

65. Higashi Y. Roles of oxidative stress and inflammation in vascular endothelial dysfunction-related disease. *Antioxid (Basel)*. (2022) 11:20220930. doi: 10.3390/antiox11101958

66. Teixeira-Lemos E, Nunes S, Teixeira F, Reis F. Regular physical exercise training assists in preventing type 2 diabetes development: focus on its antioxidant and anti-inflammatory properties. *Cardiovasc Diabetol*. (2011) 10:12. doi: 10.1186/1475-2840-10-12

67. Hambrecht R, Adams V, Erbs S, Linke A, Kränkel N, Shu Y, et al. Regular physical activity improves endothelial function in patients with coronary artery disease by increasing phosphorylation of endothelial nitric oxide synthase. *Circulation*. (2003) 107:3152–8. doi: 10.1161/01.Cir.0000074229.93804.5c

68. Vandercappellen EJ, Koster A, Savelberg H, Eussen S, Dagnelie PC, Schaper NC, et al. Sedentary behaviour and physical activity are associated with biomarkers of endothelial dysfunction and low-grade inflammation-relevance for (Pre)Diabetes: the maastricht study. *Diabetologia*. (2022) 65:777–89. doi: 10.1007/s00125-022-05651-3

69. El Assar M, Álvarez-Bustos A, Sosa P, Angulo J, Rodríguez-Mañas L. Effect of physical activity/exercise on oxidative stress and inflammation in muscle and vascular aging. *Int J Mol Sci*. (2022) 23:8713. doi: 10.3390/ijms23158713

70. Heinisch PP, Bello C, Emmert MY, Carrel T, Dreßen M, Hörer J, et al. Endothelial progenitor cells as biomarkers of cardiovascular pathologies: A narrative review. *Cells*. (2022) 11:1678. doi: 10.3390/cells11101678

71. Ribeiro F, Ribeiro IP, Alves AJ, do Céu Monteiro M, Oliveira NL, Oliveira J, et al. Effects of exercise training on endothelial progenitor cells in cardiovascular disease: A systematic review. *Am J Phys Med Rehabil*. (2013) 92:1020–30. doi: 10.1097/PHM.0b013e31829b4c4f

72. Koutroumpi M, Dimopoulos S, Psarra K, Kyprianou T, Nanas S. Circulating endothelial and progenitor cells: evidence from acute and long-term exercise effects. *World J Cardiol*. (2012) 4:312–26. doi: 10.4330/wjc.v4.i12.312

73. Ferentinos P, Tsakirides C, Swainson M, Davison A, Martyn-St James M, Ispoglou T. The impact of different forms of exercise on endothelial progenitor cells in healthy populations. *Eur J Appl Physiol*. (2022) 122:1589–625. doi: 10.1007/s00421-022-04921-7

74. Thijssen DH, Dawson EA, Black MA, Hopman MT, Cable NT, Green DJ. Brachial artery blood flow responses to different modalities of lower limb exercise. *Med Sci Sports Exerc*. (2009) 41:1072–9. doi: 10.1249/MSS.0b013e3181923957

75. Gerhold KA, Schwartz MA. Ion channels in endothelial responses to fluid shear stress. *Physiol (Bethesda)*. (2016) 31:359–69. doi: 10.1152/physiol.00007.2016

76. Currie KD, McKelvie RS, Macdonald MJ. Flow-mediated dilation is acutely improved after high-intensity interval exercise. *Med Sci Sports Exerc*. (2012) 44:2057–64. doi: 10.1249/MSS.0b013e318260ff92

77. Casey DP, Schneider AC, Ueda K. Influence of chronic endurance exercise training on conduit artery retrograde and oscillatory shear in older adults. *Eur J Appl Physiol*. (2016) 116:1931–40. doi: 10.1007/s00421-016-3445-4

78. Wisløff U, Støylen A, Loennechen JP, Bruvold M, Rognmo Ø, Haram PM, et al. Superior cardiovascular effect of aerobic interval training versus moderate continuous training in heart failure patients: A randomized study. *Circulation*. (2007) 115:3086–94. doi: 10.1161/circulationaha.106.675041

79. Lovren F, Pan Y, Quan A, Singh KK, Shukla PC, Gupta M, et al. Adropin is a novel regulator of endothelial function. *Circulation*. (2010) 122:S185–92. doi: 10.1161/circulationaha.109.931782

80. Fujie S, Hasegawa N, Sato K, Fujita S, Sanada K, Hamaoka T, et al. Aerobic exercise training-induced changes in serum adropin level are associated with reduced arterial stiffness in middle-aged and older adults. *Am J Physiol Heart Circ Physiol*. (2015) 309:H1642–7. doi: 10.1152/ajpheart.00338.2015

81. Ramos JS, Dalleck LC, Tjonna AE, Beetham KS, Coombes JS. The impact of high-intensity interval training versus moderate-intensity continuous training on vascular function: A systematic review and meta-analysis. *Sports Med*. (2015) 45:679–92. doi: 10.1007/s40279-015-0321-z

82. Fuertes-Kenneally L, Manresa-Rocamora A, Blasco-Peris C, Ribeiro F, Sempere-Ruiz N, Sarabia JM, et al. Effects and optimal dose of exercise on endothelial function in patients with heart failure: A systematic review and meta-analysis. *Sports Med Open*. (2023) 9:8. doi: 10.1186/s40798-023-00553-z

83. Izquierdo M, Merchant RA, Morley JE, Anker SD, Aprahamian I, Arai H, et al. International exercise recommendations in older adults (Icfsr): expert consensus guidelines. *J Nutr Health Aging*. (2021) 25:824–53. doi: 10.1007/s12603-021-1665-8

84. Aengevaeren VL, VAN Kimmenade RRJ, Hopman MTE, VAN Royen N, Snider JV, Januzzi JL, et al. Exercise-induced changes in soluble st2 concentrations in marathon runners. *Med Sci Sports Exerc*. (2019) 51:405–10. doi: 10.1249/mss.0000000000001806

85. Aengevaeren VL, Hopman MTE, Thijssen DHJ, van Kimmenade RR, de Boer MJ, Eijsvogels TMH. Endurance exercise-induced changes in bnp concentrations in cardiovascular patients versus healthy controls. *Int J Cardiol*. (2017) 227:430–5. doi: 10.1016/j.ijcard.2016.11.016

86. Shave R, Baggish A, George K, Wood M, Scharhag J, Whyte G, et al. Exercise-induced cardiac troponin elevation: evidence, mechanisms, and implications. *J Am Coll Cardiol*. (2010) 56:169–76. doi: 10.1016/j.jacc.2010.03.037

87. Bull FC, Al-Ansari SS, Biddle S, Borodulin K, Buman MP, Cardon G, et al. World health organization 2020 guidelines on physical activity and sedentary behaviour. *Br J Sports Med*. (2020) 54:1451–62. doi: 10.1136/bjsports-2020-102955

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Effects of aerobic and resistance exercise for 9 months on serum free light chains in type 2 diabetes

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Background and aims: Serum polyclonal free light chains (FLCs) levels are associated with overall survival in the general population, reflecting their utility as a biomarker of underlying immune activation and inflammation. Regular exercise is known to ameliorate low-grade inflammation in chronic diseases such as type 2 diabetes; however, the effects of different exercise training modalities on FLCs in adults with type 2 diabetes is unknown. This study investigated the effects of 9-month of aerobic, resistance or combined supervised exercise on serum FLCs in 164 patients with type 2 diabetes (age 58 ± 8 years; 63% female).

Methods: 164 participants from the Health Benefits of Aerobic and Resistance Training in individuals with type 2 diabetes trial (HART-D) were randomly assigned to no exercise (n = 27), aerobic exercise alone (n = 41), resistance exercise alone (n = 49), or a combination of aerobic and resistance exercise (n = 47). Fasting serum samples were collected before and after completion of the intervention to quantify changes in kappa and lambda FLCs, and serum creatinine, using commercially-available ELISAs.

Results: At baseline, combined kappa and lambda FLCs (FLC sum; calculated as kappa + lambda FLCs) were positively correlated with high-sensitive C-reactive protein (hs-CRP) (r = 0.237, p < 0.05) and fat mass (r = 0.162, p < 0.05), and negatively associated with aerobic fitness (r = −0.238, p < 0.05). While non-exercise controls exhibited an increase in FLCs over the 9-month study, exercise training blunted this increase (Δ FLC sum control arm: 3.25 ± 5.07 mg·L^{-1} vs. all exercise arms: -0.252 ± 6.60 mg·L^{-1}, p < 0.05), regardless of exercise modality.

Conclusion: Serum FLCs were associated with physical fitness and body composition in patients with type 2 diabetes. 9-month of exercise training prevented the accumulation of FLCs, regardless of exercise modality. Unlike hs-CRP—which did not change during the trial—serum FLCs may serve as a more sensitive biomarker of chronic low-grade inflammation in this population.

KEYWORDS

exercise training, free light chains, inflammation, type 2 diabetes, 9-month intervention

1 Introduction

The prevalence of type 2 diabetes has steadily increased globally over the past 30 years, and it is estimated that over 7% of the worldwide population and 15% of the United States population will have type 2 diabetes by 2030 (Rowley et al., 2017; Khan et al., 2020). Diabetes ranks in the top ten for both causes of overall mortality and burden of disease (disability-adjusted life years) (Khan et al., 2020). While the etiology of type 2 diabetes is multifaceted, it is clear that chronic activation of the immune system, and the associated chronic low-grade inflammation observed in patients with type 2 diabetes, promotes the incidence and progression of the disease (Hotamisligil, 2017). Habitual physical activity has long been advocated as a means to prevent the occurrence of type 2 diabetes (Galaviz et al., 2015), and to improve the pathophysiology of the disease such as reduced Hemoglobin A_{1c} (HbA_{1c}) (Church et al., 2010) and improved muscle metabolism (Sparks et al., 2013). However, there is still uncertainty regarding the ideal modality of exercise to improve various physiological outcomes of patients with type 2 diabetes, especially when it comes to reducing low-grade inflammation.

Biomarkers of inflammation such as circulating C-reactive protein (CRP), an indicator of innate immune activity, are known to be elevated in men and women with type 2 diabetes (Freeman et al., 2002; Nakanishi et al., 2003; Kanmani et al., 2019). However, serum CRP has been shown to exhibit profound intra- and inter-individual variability (DeGoma et al., 2012) and the mechanistic underpinnings of elevated CRP in patients with type 2 diabetes remain uncertain (Lee et al., 2009; Stanimirovic et al., 2022). To this end, novel biomarkers of inflammation such as immunoglobulin kappa and lambda free light chains (FLCs) are increasingly being explored as an alternative means of tracking chronic low-grade inflammation (Gudowska-Sawczuk and Mroczko, 2023). In healthy adults, kappa and lambda light chain isotypes are released in circulation at a steady rate of around 500 mg/day and are rapidly removed by glomerular filtration, conferring them a relatively short half-life of 2–6 h (Hutchison et al., 2014) and thus acting as a 'real-time' indicator of underlying immune-inflammatory activation relative to intact immunoglobulin, which has a much longer half-life. Excessive accumulation of FLCs during inflammation generates degranulation and synthesis of mast cells and releases further inflammatory mediators by activating neutrophils and other immune cells (Nakano et al., 2011; Braber et al., 2012). In this context, abnormal FLC accumulation has been reported to influence the pathogenesis of type 2 diabetes and is associated with cardiovascular diseases in this population (Bellary et al., 2014; Aberer et al., 2018; Matsumori et al., 2020). Therefore, excessive elevation of FLCs can be used to predict health and disease progression, and overall survival in general and patient populations (Dispenzieri et al., 2012).

Exercise is well-accepted to be a safe treatment for various chronic diseases, known for its ability to reduce inflammatory markers such as CRP, IL-6 and TNF- α (You and Nicklas, 2006; Hopps et al., 2011). In particular, combining aerobic with resistance exercise in patients with type 2 diabetes has been shown to be effective in reducing inflammatory cytokine concentrations by dramatically remodeling in body composition, to a greater extent than aerobic or resistance exercise in isolation (Balducci et al., 2010; Hopps et al., 2011). Furthermore, total FLCs concentrations are lower in healthy adults who report a greater level of physical activity than their sedentary age-matched counterparts, particularly those engaging in regular aerobic endurance exercise (Heaney et al., 2016). Given these findings, the practice of regular physical activity, especially combined aerobic and resistance exercise, may be a promising intervention to reduce low-grade inflammation and ameliorate FLC concentrations in patients with chronic inflammatory diseases. However, it is unknown: 1) whether exercise suppresses the accumulation of serum FLCs in patients with type 2 diabetes; 2) if exercise-associated changes in circulating FLCs are dependent on exercise modality and 3) if these changes are mediated by improvements in exercise performance and fitness or remodeling of body composition.

Therefore, the aim of this study was to investigate the effects of 9 months of aerobic, resistance or combined exercise on circulating FLCs in participants with type 2 diabetes. We hypothesized that: 1) FLCs would be related to physical fitness and hs-CRP, respectively, at trial entry, 2) FLCs would increase in non-exercising patients with type 2 diabetes over time, whereas patients enrolled in the exercise group would not exhibit increases in serum FLC concentrations, and 3) the degree by which circulating FLCs would change during the 9 months intervention would depend on exercise modality, with the greatest effect observed in the combined aerobic and resistance exercise group.

2 Materials and methods

2.1 Participants

The present study used archived serum samples from the HART-D study (Church et al., 2010). A total of 262 participants with type 2 diabetes and HbA_{1c} levels ranging from 6.5% to 11.0% were recruited for the parent study. All participants had a sedentary lifestyle, defined as less than 2 days per week of exercise, less than 60 min per week of aerobic exercise, and no resistance exercise. Of the 262 participants, a sub-cohort of 164 patients consented to be included in subsequent studies (mean ± SD: age 58 ± 8 years, female n = 103). Participants who did not meet the study criteria or exhibited other co-morbidities such as body mass index greater than 48.0 kg/m^2, blood pressure greater than 160/100 mmHg, fasting triglycerides greater than 500 mg/dL, urine protein greater than 100 mg/dL, serum creatinine greater than 1.5 mg/dL, and past medical history were excluded from the parent HART-D study.

2.2 Study design

Participants were randomly assigned to four groups of supervised activity for 9 months: 1) a stretching-control (n = 27), 2) aerobic (n = 41), 3) resistance (n = 49), and 4) a combination of aerobic and resistance training groups (n = 47). The control group was asked to maintain present activity and was provided with optional stretching and relaxation classes once weekly.

The aerobic training group was designed for participants to perform 12 kcal/kg of body mass of walking/jogging exercise per

week at 50%–80% of maximal oxygen consumption, and exercise volume was weight-adjusted every week. The resistance training was set to 3 days per week and consisted of 2 sets of 4 upper body exercises (bench press, seated row, shoulder press, and pull down), 3 sets of 3 lower body exercises (leg press, extension, and flexion), and 1 set each of abdominal crunches and back extensions. Each set consisted of 10–12 repetitions. The combined training was standardized to 10 kcal/kg per week of aerobic training and a single set of the same resistance exercises twice a week.

2.3 Fitness measurements

Body composition was measured by Dual-energy X-ray absorptiometry (DXA) scans using a QDR 4500A whole-body scanner (Hologic Inc., Bedford, MA). Aerobic fitness was measured using a graded exercise test on a treadmill (Trackmaster 425, Carefusion, Newton, KS).

Muscular strength measurements were performed using a Biodex System 3 dynamometer (Biodex Medical Systems, Shirley, NY). Peak torque (60°/s) and total work (300°/s) were evaluated using concentric isokinetic knee flexion and extension. Muscle quality was calculated by dividing the total amount of work performed during the 30 repetitions by the leg lean mass as determined by DXA.

2.4 Sample collection and analysis

Resting blood samples were collected at baseline and after the 9-month intervention using Serum Separating Tubes (BD Vacutainers). The serum samples were stored at −80 until analysis via commercially available ELISAs to characterize changes in kappa and lambda FLCs (Seralite; Abingdon Health, Oxford, United Kingdom) and hs-CRP (Abcam Cambridge, MS). Using published guidelines for hs-CRP (Haffner, 2006) and circulating FLCs (Heaney et al., 2020), 51.8% of participants had abnormal hs-CRP at baseline (greater than 3 $mg{\cdot}L^{-1}$), and 41.5% of participants had abnormally high levels of kappa FLC (8.72–23.0 $mg{\cdot}L^{-1}$). Creatinine and Cystatin c were measured to control for kidney function (Abcam, Cambridge, MS) according to the CKD-EPI equation (Inker et al., 2021).

2.5 Statistical analysis

All statistical analyzes were conducted using IBM SPSS Statistical Package Version 28.0 (IBM Inc., Armonk, NY). All data were assessed for homogeneity of variances using Levene's test. The concentrations of hs-CRP and FLCs between baseline and 9-month values in the control were initially compared using paired t-tests to identify changes in inflammation in type 2 diabetes patients over time. The treatment effects (group and exercise modality) on hs-CRP and FLCs were determined using a two-way repeated measures ANOVA with renal function (eGFR; estimated glomerular filtration rate) as a covariate. The relationship between circulating FLCs and hs-CRP at baseline and 9-months values along with other outcome variables were initially analyzed using Pearson's correlation. The relationship between type 2 diabetes pathophysiology, including body composition and exercise performance, along with the changes in circulating FLCs in response to the 9-month intervention were evaluated using linear regression models. The comparisons between groups, correlations, and linear regression were analyzed using the amount of change in circulating FLCs between baseline and 9-month values (Δ value; 9-month - baseline value). All results are represented as mean ± standard deviation (SD), and statistical significance was set at $p < 0.05$.

2.6 Ethics approval

All participants gave written informed consent before participating in the study. The study was approved by the Ethics Committee of Louisiana State University (IRB # E10505). The parent study was approved by the Ethics Committee of Pennington Biomedical Research Center and registered on clinicaltrials.gov under the Clinical trial reg. no. NCT00458133.

3 Results

3.1 Physical characteristics

The participants included in this study were a sub-sample of 164 participants [male: 37.20% ($n = 61$); female: 62.80% ($n = 103$)] from the HART-D study (Church et al., 2010). Participants' physical characteristics are shown in Table 1. Physical characteristics between the groups were not different ($p > 0.05$).

3.2 Correlation between FLCs and hs-CRP at baseline

The association between serum FLCs and hs-CRP at baseline were assessed using Pearson's correlations and shown in Figure 1. A positive correlation was observed between combined FLC (sum of kappa and lambda FLCs) and hs-CRP ($r = 0.237$, $p < 0.05$; Figure 1A). This appears to be explained by the positive correlation between kappa FLC and hs-CRP ($r = 0.266$, $p < 0.05$; Figure 1B), since no significant correlation was observed between lambda FLC and hs-CRP ($r = 0.112$, $p > 0.05$; Figure 1C).

3.3 Correlation between FLCs, body composition and physical fitness at baseline

Considering the impact of body composition on hs-CRP and low-grade inflammation, we investigated the correlation between FLCs levels and body composition before the start of the intervention (Table 2). Fat mass was positively correlated with combined FLC ($r = 0.162$, $p < 0.05$) and kappa FLC ($r = 0.166$, $p < 0.05$). However, circulating FLCs were not associated with any other metrics of body composition. The correlations between FLCs

TABLE 1 Baseline physical characteristics of participants.

	Total participant (n = 164)	Control (n = 27)	Aerobic (n = 41)	Resistance (n = 49)	Combination (n = 47)
Age (years)	57.6 ± 8.0	58.9 ± 8.8	56.7 ± 8.2	59.1 ± 8.1	55.9 ± 6.8
HbA_{1c} (%)	7.2 ± 1.1	7.5 ± 1.4	7.0 ± 0.9	7.1 ± 1.0	7.2 ± 1.1
Weight (kg)	95.6 ± 17.4	96.5 ± 21.2	93.5 ± 14.3	96.0 ± 16.1	96.6 ± 19.2
BMI (kg/m^2)	34.1 ± 5.7	35.0 ± 6.6	33.2 ± 5.1	33.8 ± 5.4	34.7 ± 5.9
Fat Mass (kg)	36.5 ± 10.8	38.3 ± 12.4	34.6 ± 9.1	36.2 ± 10.5	37.5 ± 11.4
Lean Mass (kg)	57.2 ± 11.4	56.2 ± 11.9	56.8 ± 11.0	58.0 ± 10.9	57.4 ± 12.3
Body Fat (%)	37.6 ± 7.6	38.9 ± 7.2	36.7 ± 7.9	37.1 ± 8.1	38.1 ± 7.1
Waist Circumference (cm)	110.5 ± 12.7	109.8 ± 15.0	108.1 ± 11.2	111.3 ± 12.2	112.2 ± 13.2
VO_{2peak} (mL/kg/min)	19.7 ± 4.4	18.9 ± 3.2	20.7 ± 5.5	19.8 ± 4.6	19.2 ± 3.4
Muscle Quality (Nm/kg)	13.2 ± 3.7	12.7 ± 2.7	13.6 ± 4.2	13.1 ± 3.7	13.2 ± 3.7

Data are mean ± SD; HbA_{1c}, Hemoglobin A_{1c}; BMI, body mass index; VO_{2peak}, peak oxygen consumption.

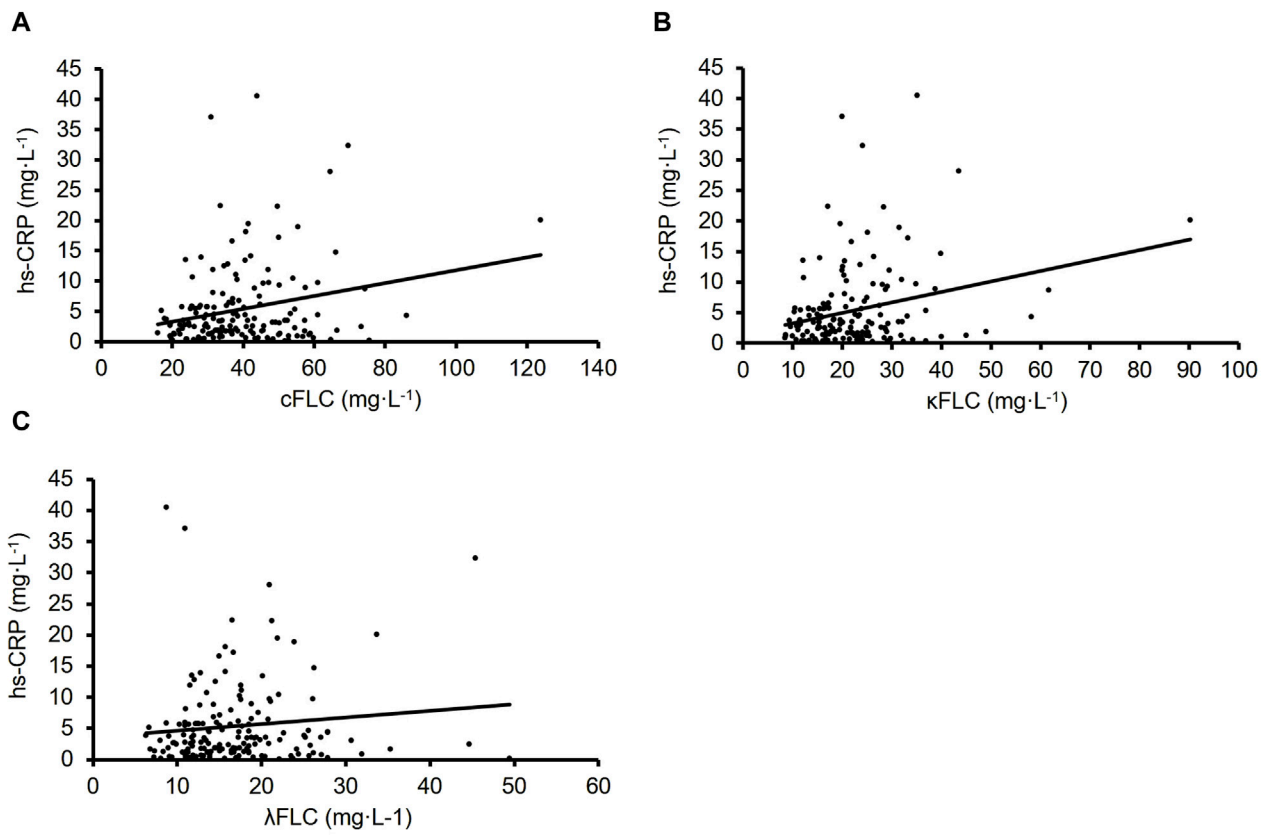

FIGURE 1
The correlation between FLCs and hs-CRP (n = 164). Combined FLC (r = 0.237, $p < 0.05$ **(A)**. Kappa FLC (r = 0.266, $p < 0.05$ **(B)**. Lambda FLC (r = 0.112, $p > 0.05$ **(C)**.

and exercise performance and fitness are shown in Table 3. FLCs were negatively correlated with muscle torque ($p < 0.05$) and VO_{2peak} ($p < 0.05$), independently of body composition as demonstrated by the similar association seen with muscle quality ($p < 0.05$) and lean mass VO_{2peak} ($p < 0.05$).

3.4 Serum FLCs increase in inactive patients with type 2 diabetes over 9 months

Changes in biomarkers of inflammation during the 9-month intervention in the control group are shown in Figure 2. Overall,

TABLE 2 Pearson's correlation between FLCs and body composition in all participants at baseline (n = 164).

	Weight		Fat Mass		Lean Mass		BMI		Waist circumference	
	r	*p*-value	*r*	*p*-value	*r*	*p*-value	*r*	*p*-value	*r*	*p*-value
Combined FLC	0.079	0.312	0.162	0.038*	−0.028	0.723	0.098	0.210	0.010	0.901
Kappa FLC	0.079	0.312	0.166	0.034*	−0.026	0.737	0.095	0.228	0.019	0.808
Lambda FLC	0.052	0.507	0.101	0.197	−0.020	0.795	0.070	0.372	−0.008	0.923

*$p < 0.05$.

TABLE 3 Pearson's correlation between FLCs and exercise performance and fitness in all participants at baseline (n = 164).

	Torque		Muscle quality		VO_{2peak}		Lean Mass VO_{2peak}	
	r	*p*-value	*r*	*p*-value	*r*	*p*-value	*r*	*p*-value
Combined FLC	-0.191	0.015*	-0.256	< 0.001*	-0.238	0.002*	-0.242	0.002*
Kappa FLC	-0.173	0.027*	-0.257	< 0.001*	-0.231	0.003*	-0.233	0.003*
Lambda FLC	-0.152	0.053	-0.168	0.031*	-0.166	0.034*	-0.172	0.028*

*$p < 0.05$.

our patient population exhibited elevated circulating hs-CRP along with kappa FLC at baseline, regardless of group. There was no difference in kappa FLC concentration between control and exercisers at baseline ($p > 0.05$), with both control and exercise participants exhibiting higher than normal levels of serum kappa FLC (frequency of participants with clinically elevated kappa FLC - control: 55.6%; exercise group: 38.7%) (Heaney et al., 2020). Interestingly, lambda FLC levels remained within the normal range for both groups. In the control group, hs-CRP was not significantly different between baseline and follow-up ($p = 0.685$; Figure 2A), however combined FLC significantly increased by 8% from 41.5 ± 15.8 mg·L^{-1} to 44.8 ± 16.1 mg·L^{-1} ($p = 0.003$; Figure 2B). This increase appears to be driven by kappa FLC which significantly increased by 11.7% from 22.3 ± 7.51 mg·L^{-1} to 24.9 ± 7.99 mg·L^{-1} ($p < 0.001$; Figure 2C), while lambda FLC levels remained unchanged at follow-up ($p = 0.187$; Figure 2D).

3.5 Serum FLCs and exercise training for 9 months

Prior to analyzing the effects of differing modalities of exercise on hs-CRP and FLCs, we characterized whether engaging in any exercise training—regardless of modality—altered circulating hs-CRP and FLCs, by comparing the inactive control groups to all the exercisers combined. The changes in FLCs and hs-CRP between the control and exercise groups in response to the 9-month intervention are shown in Figure 3. The change in hs-CRP was not significantly different between the control and exercise groups ($p = 0.613$; Figure 3A). However, the change in combined FLC in response to the 9-month exercise intervention was different between the control and exercise groups ($p = 0.010$; Figure 3B), with the change in circulating kappa FLC concentrations significantly greater in the control group than the exercisers ($p = 0.004$; Figure 3C). No differences were observed in lambda FLC between the control and exercise groups over time ($p = 0.266$; Figure 3D).

3.6 Exercise-induced changes in FLCs and hs-CRP are independent of exercise modality

A 2-way repeated measures ANOVA was used to identify the effects of the different exercise modalities on serum FLCs and hs-CRP in patients with Type 2 Diabetes, while controlling for change in renal function (ΔeGFR). The data are presented in Table 4. There was no difference in eGFR at baseline between the groups ($p > 0.05$), nor was there significant differences in eGFR in response to any of the interventions ($p > 0.05$). There was no main effect for time or group for hs-CRP (time: $p = 0.820$; group: $p = 0.513$), and time for lambda FLCs (time: $p = 0.289$). However, we observed a group × time interaction in serum kappa FLC ($p = 0.039$) independently of changes in kidney function. Considering the highly heterogenous nature of the patient population included in this study, we also assessed the effects of exercise modality on the changes in circulating FLCs and hs-CRP in response to 9 months of exercise training to control for baseline hs-CRP and FLCs concentrations. These are shown in Table 5. There was no significant difference in hs-CRP in response to the exercise intervention between exercise groups ($p = 1.000$). Similarly, the changes in combined ($p = 0.865$), kappa ($p = 0.958$), and lambda

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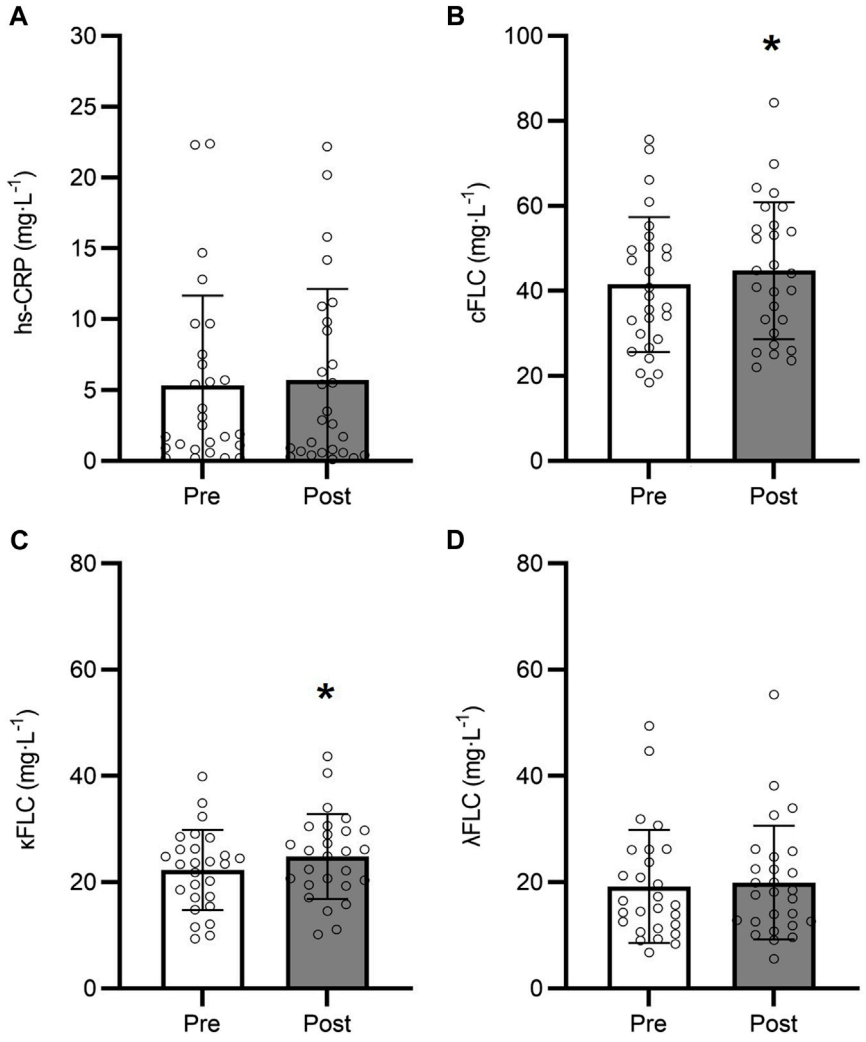

FIGURE 2
Changes in hs-CRP **(A)**, Combined FLC **(B)**, Kappa FLC **(C)**, and Lambda FLC **(D)** over the 9-month intervention in the control group (n = 27). *9-month different from baseline ($p < 0.05$). Data are presented as mean ± SD.

FLCs (p = 0.673) concentrations in response to the intervention were similar across the different exercise modalities.

3.7 Greater reductions in FLCs are associated with improved performance and fitness in all participants

Pearson's correlations were used to identify preliminary associations between changes in circulating FLCs levels and changes in aerobic fitness and muscle strength following the 9 months intervention (Table 6). The change in combined FLCs were negatively correlated with the changes in torque (r = −0.172, p = 0.028) and muscle quality (r = −0.169, p = 0.031) in response to the intervention. This appears to be driven by lambda FLC since the changes to lambda FLC were also negatively correlated with changes in torque (r = −0.197, p = 0.012) and muscle quality (r = −0.188, p = 0.016). However, kappa FLC was not correlated with changes in exercise performance and fitness.

3.8 Greater reductions in FLCs are associated with greater improvements in performance amongst exercisers

The correlation between the change in FLCs and exercise performance over the 9-month intervention in all exercisers is shown in Table 7. Intervention-induced change in lambda FLC were negatively correlated with the changes in torque (r = −0.192, p = 0.025) and muscle quality (r = −0.196, p = 0.022) in response to the 9 months intervention. Combined and kappa FLCs were not correlated with any other exercise performance metrics.

3.9 Independent variables explaining the changes in FLCs in response to the intervention

Considering the bi-directional impact of inflammation on type 2 diabetes pathophysiology, we attempted to further investigate the

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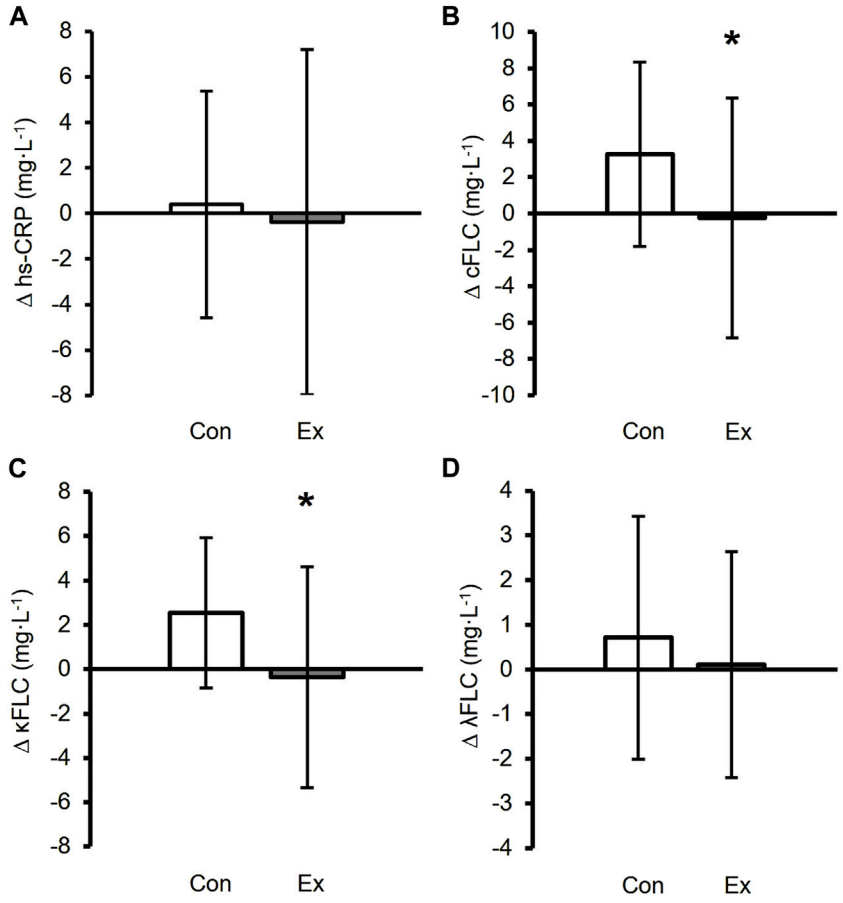

FIGURE 3
Changes in inflammatory biomarkers between the control in white (n = 27) and exercise groups in black (n = 137). Δ values were calculated as 9-month value - baseline. Δ hs-CRP **(A)**, Δ Combined FLC **(B)**, Δ Kappa FLC **(C)**, and Δ Lambda FLC **(D)** in the control group. *Exercise group was a significant difference compared to the control group ($p < 0.05$). Data are presented as mean ± SD.

relationship between serum FLCs and outcomes related to the etiology of type 2 diabetes by performing multiple linear regression analysis (Table 8). The independent variables included were baseline age, sex, duration of diabetes (DB duration), kidney function using eGFR, and Δ fat mass, Δ torque, Δ muscle quality, Δ VO_{2peak}, and Δ lean mass VO_{2peak}. When age, sex, DB duration, eGFR and changes in body composition and performance were included, change in fat mass significantly explained the changes in kappa FLC (Model 2, β = 0.327, R^2 = 0.074, p = 0.022; Model 3, β = 0.343, R^2 = 0.065, p = 0.025; Model 4, β = 0.348, R^2 = 0.065, p = 0.016) between baseline and follow-up. Out of the different outcomes of performance, only the improvements in muscle quality in response to the exercise intervention significantly explained the changes in lambda FLC (Model 2, β = −0.186, R^2 = 0.059, p = 0.029). To identify the individual effect of the performance variables on the exercise group, multiple sub-models were run with a unique performance factor included in each (Table 9). In all models, age was a significant predictor of Δ kappa FLC concentration, with older participants exhibiting a greater reduction in kappa FLC than their younger counterparts (Model 5, β = −0.121, R^2 = 0.063, p = 0.050; Model 6, β = −0.120, R^2 = 0.062, p = 0.041; Model 7, β = −0.122, R^2 = 0.061, p = 0.040; Model 8, β = −0.121, R^2 = 0.061, p = 0.039). Conversely, sex was significantly associated with the change in lambda FLC in response to the intervention, with men exhibiting a greater decrease in lambda FLC over the 9 months intervention than women (Model 5, β = 0.951, R^2 = 0.089, p = 0.040; Model 7, β = 0.931, R^2 = 0.054, p = 0.041; Model 8, β = 0.926, R^2 = 0.054, p = 0.041). Finally, participants who exhibited greater improvements in muscle quality also showed the greatest reductions in lambda FLC (Model 6, β = −0.179, R^2 = 0.082, p = 0.050).

4 Discussion

Physical inactivity and sedentary behaviors are known for promoting the occurrence and progression of type 2 diabetes (Hamilton et al., 2014), and systemic low-grade inflammation (Falconer et al., 2014). Numerous studies have advocated for using exercise to prevent type 2 diabetes, and to improve clinical outcomes of patients with type 2 diabetes (Sigal et al., 2006; Jorge et al., 2011). However, the impact of different exercise modalities on biomarkers of inflammation in individuals with type 2 diabetes remain mostly unclear. In this context, this study investigated the effects of a 9-month exercise intervention that included aerobic

TABLE 4 Mean serum FLCs and hs-CRP response in each condition. The interaction effects from the two-way repeated measures ANOVA for time (9-months) and group (exercise modality) on FLCs and hs-CRP are reported after controlling for changes in kidney function during the intervention (ΔeGFR).

	Aerobic (*n* = 41)		Resistance (*n* = 49)		Combination (*n* = 47)		Control (*n* = 27)		Interaction (*time x group*)	
	Baseline	9-month	Baseline	9-month	Baseline	9-month	Baseline	9-month	*F*	*p*
Hs-CRP ($mg{\cdot}L^{-1}$)	5.12 ± 7.2	4.75 ± 5.8	4.40 ± 5.7	4.00 ± 5.6	6.59 ± 7.4	6.21 ± 11.0	5.33 ± 6.3	5.72 ± 6.4	0.103	0.958
Combined FLC ($mg{\cdot}L^{-1}$)	38.73 ± 14.1	38.04 ± 15.5	36.82 ± 11.9	36.59 ± 11.9	40.04 ± 18.1	40.14 ± 15.4	41.50 ± 15.8	44.76 ± 16.1	2.338	0.076
Kappa FLC ($mg{\cdot}L^{-1}$)	22.60 ± 11.2	22.11 ± 12.2	21.45 ± 8.7	21.03 ± 8.4	22.40 ± 12.8	22.23 ± 10.1	22.31 ± 7.5	24.85 ± 8.0	2.863	0.039*
Lambda FLC ($mg{\cdot}L^{-1}$)	16.12 ± 5.3	15.93 ± 5.7	15.36 ± 4.6	15.56 ± 5.0	17.64 ± 7.6	17.91 ± 7.7	19.20 ± 10.6	19.91 ± 10.7	0.634	0.594

Data are presented as mean ± SD. * time × group interaction effect ($p < 0.05$).

TABLE 5 Changes in FLCs and hs-CRP by exercise type (*n* = 137) or control (*n* = 27).

	Aerobic (*n* = 41)	Resistance (*n* = 49)	Combination (*n* = 47)	Control (*n* = 27)
Δ hs-CRP ($mg{\cdot}L^{-1}$)	−0.37 ± 6.0	−0.39 ± 4.1	−0.37 ± 11.0	0.39 ± 5.0
Δ Combined FLC ($mg{\cdot}L^{-1}$)	−0.69 ± 6.0	−0.23 ± 5.3	0.10 ± 8.2	3.25 ± 5.1*
Δ Kappa FLC ($mg{\cdot}L^{-1}$)	−0.50 ± 4.3	−0.43 ± 4.1	−0.17 ± 6.3	2.54 ± 3.4*
Δ Lambda FLC ($mg{\cdot}L^{-1}$)	−0.19 ± 2.6	0.20 ± 2.2	0.27 ± 2.8	0.71 ± 2.7

Data are presented as mean ± SD; Δ values were calculated as 9-month value - baseline. *9-month different from baseline ($p < 0.05$).

TABLE 6 Pearson's correlation between changes in FLCs and changes in exercise performance and fitness (*n* = 164).

	Δ Torque		Δ Muscle quality		Δ VO_{2peak}		Δ Lean Mass VO_{2peak}	
	r	*p*-value	*r*	*p*-value	*r*	*p*-value	*r*	*p*-value
Δ Combined FLC	−0.172	0.028*	−0.169	0.031*	−0.039	0.621	−0.009	0.908
Δ Kappa FLC	−0.125	0.111	−0.126	0.107	−0.060	0.448	−0.022	0.783
Δ Lambda FLC	−0.197	0.012*	−0.188	0.016*	0.015	0.850	0.018	0.817

Δvalues were calculated as 9-month value - baseline. *$p < 0.05$.

TABLE 7 Pearson's correlation between FLCs and performance based on exercise group (*n* = 137).

	Δ Torque		Δ Muscle quality		Δ VO_{2peak}		Δ Lean Mass VO_{2peak}	
	r	*p*-value	*r*	*p*-value	*r*	*p*-value	*r*	*p*-value
Δ Combined FLC	−0.133	0.121	−0.134	0.119	0.006	0.948	0.022	0.796
Δ Kappa FLC	−0.079	0.361	−0.078	0.367	0.003	0.976	0.030	0.726
Δ Lambda FLC	−0.192	0.025*	−0.196	0.022*	0.010	0.911	−0.001	0.986

Δvalues were calculated as 9-month value - baseline. *$p < 0.05$.

exercise alone, resistance exercise alone, or a combination of aerobic and resistance exercise on circulating free light chains (FLCs) in this patient population. We found that serum FLCs are correlated with hs-CRP, an established biomarker of inflammation in this population (Swift et al., 2012; Burmeister et al., 2014). However, while hs-CRP did not increase in the non-exercising control group

TABLE 8 Independent variables affecting the FLCs in all participants (n = 164).

Model 1	Δ Combined FLC		Δ Kappa FLC		Δ Lambda FLC	
	β ± SE	*p*-value	β ± SE	*p*-value	β ± SE	*p*-value
Age	−0.070 ± 0.077	0.363	−0.047 ± 0.057	0.412	−0.023 ± 0.031	0.459
Sex	1.035 ± 1.526	0.499	0.214 ± 1.145	0.852	0.822 ± 0.608	0.178
DB Duration	−0.052 ± 0.091	0.571	−0.063 ± 0.069	0.361	0.011 ± 0.036	0.763
eGFR	0.005 ± 0.019	0.775	0.008 ± 0.014	0.573	−0.003 ± 0.008	0.730
Δ Fat Mass	0.456 ± 0.277	0.102	0.394 ± 0.208	0.060	0.062 ± 0.110	0.575
Δ Torque	−0.063 ± 0.072	0.384	−0.041 ± 0.054	0.456	−0.023 ± 0.029	0.434
Δ Muscle Quality	0.179 ± 0.693	0.796	0.170 ± 0.520	0.743	0.009 ± 0.276	0.975
Δ VO_{2peak}	0.476 ± 0.994	0.633	0.235 ± 0.746	0.753	0.241 ± 0.396	0.543
Δ Lean Mass VO_{2peak}	−0.244 ± 0.599	0.684	−0.130 ± 0.450	0.774	−0.114 ± 0.239	0.632
Model 2	**Δ Combined FLC**		**Δ Kappa FLC**		**Δ Lambda FLC**	
	β ± SE	*p*-value	β ± SE	*p*-value	β ± SE	*p*-value
Age	−0.069 ± 0.073	0.344	−0.044 ± 0.055	0.418	−0.025 ± 0.029	0.394
Sex	1.222 ± 1.496	0.415	0.342 ± 1.121	0.761	0.880 ± 0.596	0.142
DB Duration	−0.063 ± 0.090	0.485	−0.070 ± 0.067	0.304	0.007 ± 0.036	0.855
eGFR	0.004 ± 0.019	0.832	0.007 ± 0.014	0.606	−0.003 ± 0.007	0.663
Δ Fat Mass	0.326 ± 0.188	0.085	0.327 ± 0.141	0.022*	0.000 ± 0.075	0.998
Δ Muscle Quality	−0.381 ± 0.212	0.074	−0.195 ± 0.159	0.222	−0.186 ± 0.084	0.029*
Model 3	**Δ Combined FLC**		**Δ Kappa FLC**		**Δ Lambda FLC**	
	β ± SE	*p*-value	β ± SE	*p*-value	β ± SE	*p*-value
Age	−0.085 ± 0.074	0.255	−0.053 ± 0.055	0.337	−0.032 ± 0.030	0.292
Sex	1.469 ± 1.507	0.331	0.462 ± 1.124	0.682	1.007 ± 0.603	0.097
DB Duration	−0.061 ± 0.091	0.506	−0.068 ± 0.068	0.314	0.008 ± 0.036	0.829
eGFR	0.001 ± 0.019	0.952	0.006 ± 0.014	0.680	−0.005 ± 0.008	0.538
Δ Fat Mass	0.370 ± 0.203	0.071	0.343 ± 0.152	0.025*	0.027 ± 0.081	0.744
Δ VO_{2peak}	−0.006 ± 0.234	0.981	−0.020 ± 0.175	0.910	0.014 ± 0.094	0.879
Model 4	**Δ Combined FLC**		**Δ Kappa FLC**		**Δ Lambda FLC**	
	β ± SE	*p*-value	β ± SE	*p*-value	β ± SE	*p*-value
Age	−0.084 ± 0.074	0.254	−0.053 ± 0.055	0.339	−0.032 ± 0.030	0.285
Sex	1.472 ± 1.507	0.330	0.465 ± 1.123	0.679	1.007 ± 0.603	0.097
DB Duration	−0.060 ± 0.091	0.506	−0.068 ± 0.068	0.315	0.008 ± 0.036	0.830
eGFR	0.001 ± 0.019	0.952	0.006 ± 0.014	0.679	−0.005 ± 0.008	0.536
Δ Fat Mass	0.372 ± 0.192	0.054	0.348 ± 0.143	0.016*	0.024 ± 0.077	0.753
Δ Lean Mass VO_{2peak}	0.002 ± 0.142	0.991	−0.008 ± 0.106	0.943	0.009 ± 0.057	0.872

DB, duration, duration of diabetes; eGFR, estimated glomerular filtration rate. *$p < 0.05$.

over the 9-month intervention, we observed an increase in serum FLCs. While our results confirm findings from other groups that identified the relationship between type 2 diabetes and FLCs (Matsumori et al., 2020; Matsumori, 2022), this is the first study to show that all exercise training is able to prevent the increase in circulating FLCs, thus advocating for benefits of exercise, regardless

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TABLE 9 Independent variable affecting the FLCs in the exercise groups only (n = 137).

Model 5	Δ Combined FLC		Δ Kappa FLC		Δ Lambda FLC	
	β ± SE	*p*-value	β ± SE	*p*-value	β ± SE	*p*-value
Age	−0.135 ± 0.081	0.095	−0.121 ± 0.061	0.050*	−0.015 ± 0.031	0.627
Sex	1.249 ± 1.211	0.304	0.298 ± 0.916	0.745	0.951 ± 0.459	0.040*
DB Duration	−0.019 ± 0.102	0.852	−0.028 ± 0.077	0.714	0.009 ± 0.039	0.811
eGFR	−0.006 ± 0.014	0.649	−0.001 ± 0.011	0.939	−0.006 ± 0.005	0.297
Δ Fat Mass	0.327 ± 0.317	0.305	0.285 ± 0.240	0.237	0.042 ± 0.120	0.726
Δ Torque	−0.020 ± 0.083	0.806	−0.017 ± 0.063	0.788	−0.004 ± 0.031	0.911
Δ Muscle Quality	−0.078 ± 0.790	0.921	0.086 ± 0.597	0.886	−0.164 ± 0.299	0.586
Δ VO_{2peak}	0.318 ± 1.102	0.773	−0.076 ± 0.834	0.928	0.394 ± 0.418	0.348
Δ Lean Mass VO_{2peak}	−0.156 ± 0.669	0.816	0.064 ± 0.506	0.899	−0.220 ± 0.254	0.387
Model 6	**Δ Combined FLC**		**Δ Kappa FLC**		**Δ Lambda FLC**	
	β ± SE	*p*-value	β ± SE	*p*-value	β ± SE	*p*-value
Age	−0.142 ± 0.077	0.066	−0.120 ± 0.058	0.041*	−0.022 ± 0.029	0.448
Sex	1.239 ± 1.165	0.290	0.364 ± 0.881	0.680	0.875 ± 0.443	0.051
DB Duration	−0.023 ± 0.100	0.821	−0.030 ± 0.076	0.698	0.007 ± 0.038	0.860
eGFR	−0.006 ± 0.014	0.642	−0.001 ± 0.010	0.908	−0.005 ± 0.005	0.323
Δ Fat Mass	0.258 ± 0.227	0.258	0.291 ± 0.171	0.091	−0.034 ± 0.086	0.695
Δ Muscle Quality	−0.248 ± 0.238	0.299	−0.069 ± 0.180	0.703	−0.179 ± 0.091	0.050*
Model 7	**Δ Combined FLC**		**Δ Kappa FLC**		**Δ Lambda FLC**	
	β ± SE	*p*-value	β ± SE	*p*-value	β ± SE	*p*-value
Age	−0.151 ± 0.078	0.054	−0.122 ± 0.059	0.040*	−0.029 ± 0.030	0.330
Sex	1.319 ± 1.172	0.262	0.389 ± 0.883	0.661	0.931 ± 0.451	0.041*
DB Duration	−0.021 ± 0.101	0.834	−0.029 ± 0.076	0.703	0.008 ± 0.039	0.840
eGFR	−0.008 ± 0.014	0.565	−0.002 ± 0.010	0.872	−0.006 ± 0.005	0.238
Δ Fat Mass	0.290 ± 0.235	0.220	0.302 ± 0.177	0.091	−0.012 ± 0.090	0.894
Δ VO_{2peak}	0.020 ± 0.253	0.938	0.011 ± 0.191	0.954	0.009 ± 0.097	0.929
Model 8	**Δ Combined FLC**		**Δ Kappa FLC**		**Δ Lambda FLC**	
	β ± SE	*p*-value	β ± SE	*p*-value	β ± SE	*p*-value
Age	−0.152 ± 0.077	0.052	−0.121 ± 0.058	0.039*	−0.030 ± 0.030	0.311
Sex	1.315 ± 1.169	0.263	0.389 ± 0.881	0.660	0.926 ± 0.449	0.041*
DB Duration	−0.021 ± 0.101	0.833	−0.029 ± 0.076	0.703	0.008 ± 0.039	0.842
eGFR	−0.008 ± 0.014	0.565	−0.002 ± 0.010	0.869	−0.006 ± 0.005	0.243
Δ Fat Mass	0.286 ± 0.227	0.210	0.301 ± 0.171	0.081	−0.015 ± 0.087	0.865
Δ Lean Mass VO_{2peak}	0.011 ± 0.154	0.945	0.016 ± 0.116	0.894	−0.005 ± 0.059	0.936

DB, duration, duration of diabetes; eGFR, estimated glomerular filtration rate. *$p < 0.05$.

of modality. Finally, this study highlighted that exercise-mediated improvements in fat mass and muscle quality in patients with type 2 diabetes may drive the amelioration of serum FLCs.

Chronic low-grade inflammation plays a preponderant role in the occurrence and progression of type 2 diabetes (Wang et al., 2013). The pro-inflammatory milieu seen in patients is believed to be at least partially linked to excess body fat (van Greevenbroek et al., 2013), and associated elevations in circulating pro-inflammatory cytokines and adipokines (Burhans et al., 2018), by dysregulating insulin production by beta cells in the pancreas (Esser et al., 2014). In addition to impairing insulin production, the chronic release of pro-inflammatory cytokine activates the JUN N-terminal kinase (JNK) and NF-κB pathways, which leads to B-cell activation by binding to the immunoglobulin kappa light chain gene enhancer (Donath and Shoelson, 2011; Matsumori, 2022). Since FLCs are byproducts of antibody production, circulating FLCs have been postulated to act as a biomarker of chronic inflammation in patients with type 2 diabetes (Matsumori et al., 2020), and a potential surrogate measure of insulin sensitivity. In this study, we found a low-level relationship between hs-CRP and FLCs, specifically kappa and combined FLCs, regardless of disease duration. This modest correlation between hs-CRP and FLCs observed in this population of patients was similar to the correlation between CRP and FLCs reported by other groups in patients with inflammatory diseases such as kidney disease (Burmeister et al., 2014; Assi et al., 2015). Notably, other studies focusing on acute inflammatory diseases, such as heart disease, have failed to report similar correlations between combined FLC and hs-CRP (Jackson et al., 2015). Considering the differences in disease etiology and nature of the low-grade inflammatory state between acute and chronic inflammatory diseases, this advocates for the greater sensitivity of serum FLCs in characterizing chronic low-grade inflammation in type 2 diabetes as opposed to hs-CRP which is also related to the inflammatory response of acute disease and acute exercise (Kasapis and Thompson, 2005; Hutchison and Landgren, 2011). Therefore, FLCs can be used as an indicator of chronic inflammation and help predict disease progression and survival risk (Dispenzieri et al., 2012).

Sedentary behavior and the associated accumulation in visceral adiposity lead to increases in cytokines and inflammatory markers such as IL-6 and CRP (Kriketos et al., 2004), especially in patients with type 2 diabetes (Amanat et al., 2020). In the current study, serum FLCs in the non-exercising control group increased by 8% and 11.7% for combined and kappa FLCs, respectively, over the 9 months intervention. Since the increased level of basal inflammation has been associated with worsening of type 2 diabetes (Barbarroja et al., 2012), this is of great clinical relevance. Interestingly, we did not observe significant changes in HbA_{1c} over the 9 months study period, nor did we find an association between HbA_{1c} changes and changes in FLCs concentration. This is in accordance with previously published report highlighting those patients with type 2 diabetes treated with IL-1β-inhibitors exhibit reductions in hs-CRP and IL-6 without changes in HbA_{1c} (Everett et al., 2018). Since elevated hs-CRP are associated with increased risks of type 2 diabetes worsening (Esser et al., 2014), reduction in chronic low-grade inflammation likely precedes changes in the disease pathophysiology. Further, our results appear to indicate that circulating FLCs could precede the increase in hs-CRP in this patient population. While future studies are required to confirm any causality, it could be hypothesized that circulating FLCs may increase at a faster rate than the deterioration of type 2 diabetes pathophysiological index. Furthermore, circulating CRP has been suggested to be more related to body composition than type 2 diabetes pathophysiology, since some studies failed to show an association between elevated CRP and type 2 diabetes severity when adjusting for adipose tissue mass (Deacon and Ebringer, 1976; Lee et al., 2009), which limits its sensitivity as a biomarker for monitoring chronic inflammation (Burmeister et al., 2014). This is supported by studies showing that circulating FLCs are a more sensitive biomarker of systemic inflammation than hs-CRP in other inflammatory diseases such as chronic kidney disease (Assi et al., 2015).

Lastly, we identified that changes in circulating FLCs in response to 9-month of exercise were mostly explained by changes in body fat mass. In this study, continuous long-term exercise reduced the fat mass by 3.6% from 36.1 ± 10.4 kg to 34.8 ± 10.1 kg, which was predictive of a decrease in combined and kappa FLCs. Higher fat mass has been reported to be closely related to insulin resistance and chronic inflammation in patients with type 2 diabetes (Annibalini et al., 2017). Furthermore, adipose tissue is known to be involved in the increase of pro-inflammatory cytokines and chemokines (Esser et al., 2014; Tsalamandris et al., 2019). Especially, excess visceral adiposity has been reported to potentially aggravate systemic inflammation by activating inflammatory pathways and immune cells including B-cell, and secreting inflammatory cytokines (Pedersen, 2017). Therefore, long-term exercise likely decreases fat mass in diabetic patients, thereby reducing FLCs and systemic inflammation by limiting B-cell activation and cytokine release from adipose tissue (Swift et al., 2012).

Finally, age and sex were associated with kappa and lambda FLCs respectively. Older participants exhibited greater diminutions in kappa FLC concentration in response to the 9-month intervention, when compared to their younger counterparts. As aforementioned, older participants lived with type 2 diabetes for longer than the younger patients in our cohort, and aging can induce FLCs accumulation regardless of disease status, so exercise would lead to greater improvements in this population. Regarding the gender effects described in this study, men exhibited greater reductions in circulating FLCs in response to the exercise intervention than women, regardless of exercise modality. While this study was not designed to investigate sex differences in FLCs concentrations before and after a 9-month exercise intervention, it can be postulated that this difference could be due to the slightly greater, albeit non-significant increase in muscle mass observed in men than in women.

The current study is not without limitations. Indeed, the analysis utilized archived serum samples from a large-scale clinical trial (HART-D study) designed to include heterogenous participants with various type 2 diabetes pathophysiology, duration of type 2 diabetes, medication types, and intake duration. These factors could have affected the chronic low-grade inflammation and exercise intervention effectiveness described in the present study (Boulé et al., 2011; Donath, 2014). Future studies should attempt to control for this variability to better understand the effects of exercise on soluble immunity and inflammation in patients with type 2 diabetes.

In conclusion, the results of this study showed that FLCs were associated with hs-CRP in patients with type 2 diabetes and may be sensitive at detecting lifestyle changes. Indeed, long-term sustained exercise dampened the accumulation of FLCs, regardless of modality—whereas hs-CRP did not change. These beneficial effects of exercise on FLCs appear to be mostly mediated by changes in body composition. The management of FLCs based on continuous exercise is expected to be effective in preventing or reducing the progression of type 2 diabetes and associated chronic low-grade inflammation.

Data availability statement

The raw data supporting the conclusion of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by the Pennington Biomedical Research Center and LSU IRB. The studies were conducted in accordance with the local legislation and institutional requirements. The human samples used in this study were acquired from primarily isolated as part of your previous study for which ethical approval was obtained. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

YK: Writing–original draft, Writing–review and editing, Formal Analysis. JC: Conceptualization, Formal Analysis, Methodology, Writing–review and editing. NJ: Conceptualization, Methodology, Writing–review and editing, Data curation, Investigation. TC: Conceptualization, Writing–review and editing. Eunhan Cho: Writing–review and editing, Data curation, Validation. JH: Writing–review and editing. GS: Conceptualization, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Writing–original draft, Writing–review and editing, Validation.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

Aberer, F., Tripolt, N. J., Scharnagl, H., Zedler, J., Eder, M., Oulhaj, A., et al. (2018). Combined serum free light chain levels are associated with carotid atherosclerosis in type 2 diabetes mellitus. *Diab Vasc. Dis. Res.* 15 (2), 162–164. doi:10.1177/1479164117743939

Amanat, S., Ghahri, S., Dianatinasab, A., Fararouei, M., and Dianatinasab, M. (2020). Exercise and type 2 diabetes. *Adv. Exp. Med. Biol.* 1228, 91–105. doi:10.1007/978-981-15-1792-1_6

Annibalini, G., Lucertini, F., Agostini, D., Vallorani, L., Gioacchini, A., Barbieri, E., et al. (2017). Concurrent aerobic and resistance training has anti-inflammatory effects and increases both plasma and leukocyte levels of IGF-1 in late middle-aged type 2 diabetic patients. *Oxid. Med. Cell Longev.* 2017, 3937842. doi:10.1155/2017/3937842

Assi, L. K., Mcintyre, N., Fraser, S., Harris, S., Hutchison, C. A., Mcintyre, C. W., et al. (2015). The association between polyclonal combined serum free light chain concentration and mortality in individuals with early chronic kidney disease. *PLoS One* 10 (7), e0129980. doi:10.1371/journal.pone.0129980

Balducci, S., Zanuso, S., Nicolucci, A., Fernando, F., Cavallo, S., Cardelli, P., et al. (2010). Anti-inflammatory effect of exercise training in subjects with type 2 diabetes and the metabolic syndrome is dependent on exercise modalities and independent of weight loss. *Nutr. Metab. Cardiovasc Dis.* 20 (8), 608–617. doi:10.1016/j.numecd.2009.04.015

Barbarroja, N., Lopez-Pedrera, C., Garrido-Sanchez, L., Mayas, M. D., Oliva-Olivera, W., Bernal-Lopez, M. R., et al. (2012). Progression from high insulin resistance to type 2 diabetes does not entail additional visceral adipose tissue inflammation. *PLoS One* 7 (10), e48155. doi:10.1371/journal.pone.0048155

Bellary, S., Faint, J. M., Assi, L. K., Hutchison, C. A., Harding, S. J., Raymond, N. T., et al. (2014). Elevated serum free light chains predict cardiovascular events in type 2 diabetes. *Diabetes Care* 37 (7), 2028–2030. doi:10.2337/dc13-2227

Boulé, N. G., Robert, C., Bell, G. J., Johnson, S. T., Bell, R. C., Lewanczuk, R. Z., et al. (2011). Metformin and exercise in type 2 diabetes: examining treatment modality interactions. *Diabetes Care* 34 (7), 1469–1474. doi:10.2337/dc10-2207

Braber, S., Thio, M., Blokhuis, B. R., Henricks, P. A., Koelink, P. J., Groot Kormelink, T., et al. (2012). An association between neutrophils and immunoglobulin free light chains in the pathogenesis of chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* 185 (8), 817–824. doi:10.1164/rccm.201104-0761OC

Burhans, M. S., Hagman, D. K., Kuzma, J. N., Schmidt, K. A., and Kratz, M. (2018). Contribution of adipose tissue inflammation to the development of type 2 diabetes mellitus. *Compr. Physiol.* 9 (1), 1–58. doi:10.1002/cphy.c170040

Burmeister, A., Assi, L. K., Ferro, C. J., Hughes, R. G., Barnett, A. H., Bellary, S., et al. (2014). The relationship between high-sensitivity CRP and polyclonal free light chains as markers of inflammation in chronic disease. *Int. J. Lab. Hematol.* 36 (4), 415–424. doi:10.1111/ijlh.12159

Church, T. S., Blair, S. N., Cocreham, S., Johannsen, N., Johnson, W., Kramer, K., et al. (2010). Effects of aerobic and resistance training on hemoglobin A1c levels in patients with type 2 diabetes: a randomized controlled trial. *Jama* 304 (20), 2253–2262. doi:10.1001/jama.2010.1710

Deacon, N. J., and Ebringer, A. (1976). Effect of haemolysis on plasms and serum immunoglobulin estimations. *Experientia* 32 (3), 384–386. doi:10.1007/bf01940853

Degoma, E. M., French, B., Dunbar, R. L., Allison, M. A., Mohler, E. R., 3rd, and Budoff, M. J. (2012). Intraindividual variability of C-reactive protein: the multi-ethnic study of atherosclerosis. *Atherosclerosis* 224 (1), 274–279. doi:10.1016/j.atherosclerosis.2012.07.017

Dispenzieri, A., Katzmann, J. A., Kyle, R. A., Larson, D. R., Therneau, T. M., Colby, C. L., et al. (2012). Use of nonclonal serum immunoglobulin free light chains to predict overall survival in the general population. *Mayo Clin. Proc.* 87 (6), 517–523. doi:10.1016/j.mayocp.2012.03.009

Donath, M. Y. (2014). Targeting inflammation in the treatment of type 2 diabetes: time to start. *Nat. Rev. Drug Discov.* 13 (6), 465–476. doi:10.1038/nrd4275

Donath, M. Y., and Shoelson, S. E. (2011). Type 2 diabetes as an inflammatory disease. *Nat. Rev. Immunol.* 11 (2), 98–107. doi:10.1038/nri2925

Esser, N., Legrand-Poels, S., Piette, J., Scheen, A. J., and Paquot, N. (2014). Inflammation as a link between obesity, metabolic syndrome and type 2 diabetes. *Diabetes Res. Clin. Pract.* 105 (2), 141–150. doi:10.1016/j.diabres.2014.04.006

Everett, B. M., Donath, M. Y., Pradhan, A. D., Thuren, T., Pais, P., Nicolau, J. C., et al. (2018). Anti-inflammatory therapy with canakinumab for the prevention and management of diabetes. *J. Am. Coll. Cardiol.* 71 (21), 2392–2401. doi:10.1016/j.jacc.2018.03.002

Falconer, C. L., Cooper, A. R., Walhin, J. P., Thompson, D., Page, A. S., Peters, T. J., et al. (2014). Sedentary time and markers of inflammation in people with newly diagnosed type 2 diabetes. *Nutr. Metab. Cardiovasc Dis.* 24 (9), 956–962. doi:10.1016/j.numecd.2014.03.009

Freeman, D. J., Norrie, J., Caslake, M. J., Gaw, A., Ford, I., Lowe, G. D., et al. (2002). C-reactive protein is an independent predictor of risk for the development of diabetes in the West of Scotland Coronary Prevention Study. *Diabetes* 51 (5), 1596–1600. doi:10.2337/diabetes.51.5.1596

Galaviz, K. I., Narayan, K. M. V., Lobelo, F., and Weber, M. B. (2015). Lifestyle and the prevention of type 2 diabetes: a status report. *Am. J. Lifestyle Med.* 12 (1), 4–20. doi:10.1177/1559827615619159

Gudowska-Sawczuk, M., and Mroczko, B. (2023). Free light chains κ and λ as new biomarkers of selected diseases. *Int. J. Mol. Sci.* 24 (11), 9531. doi:10.3390/ijms24119531

Haffner, S. M. (2006). The metabolic syndrome: inflammation, diabetes mellitus, and cardiovascular disease. *Am. J. Cardiol.* 97 (2), 3A–11A. doi:10.1016/j.amjcard.2005.11.010

Hamilton, M. T., Hamilton, D. G., and Zderic, T. W. (2014). Sedentary behavior as a mediator of type 2 diabetes. *Med. Sport Sci.* 60, 11–26. doi:10.1159/000357332

Heaney, J. L., Phillips, A. C., Drayson, M. T., and Campbell, J. P. (2016). Serum free light chains are reduced in endurance trained older adults: evidence that exercise training may reduce basal inflammation in older adults. *Exp. Gerontol.* 77, 69–75. doi:10.1016/j.exger.2016.02.011

Heaney, J. L. J., Campbell, J. P., Goodall, M., Plant, T., Shemar, M., Hand, C., et al. (2020). Analytical validation of new ELISAs for the quantitation of polyclonal free light chains and comparison to existing assays for healthy and patient samples. *J. Immunol. Methods* 478, 112713. doi:10.1016/j.jim.2019.112713

Hopps, E., Canino, B., and Caimi, G. (2011). Effects of exercise on inflammation markers in type 2 diabetic subjects. *Acta Diabetol.* 48 (3), 183–189. doi:10.1007/s00592-011-0278-9

Hotamisligil, G. S. (2017). Inflammation, metaflammation and immunometabolic disorders. *Nature* 542 (7640), 177–185. doi:10.1038/nature21363

Hutchison, C. A., Burmeister, A., Harding, S. J., Basnayake, K., Church, H., Jesky, M. D., et al. (2014). Serum polyclonal immunoglobulin free light chain levels predict mortality in people with chronic kidney disease. *Mayo Clin. Proc.* 89 (5), 615–622. doi:10.1016/j.mayocp.2014.01.028

Hutchison, C. A., and Landgren, O. (2011). Polyclonal immunoglobulin free light chains as a potential biomarker of immune stimulation and inflammation. *Clin. Chem.* 57 (10), 1387–1389. doi:10.1373/clinchem.2011.169433

Inker, L. A., Eneanya, N. D., Coresh, J., Tighiouart, H., Wang, D., Sang, Y., et al. (2021). New creatinine- and Cystatin C-based equations to estimate GFR without race. *N. Engl. J. Med.* 385 (19), 1737–1749. doi:10.1056/NEJMoa2102953

Jackson, C. E., Haig, C., Welsh, P., Dalzell, J. R., Tsorlalis, I. K., Mcconnachie, A., et al. (2015). Combined free light chains are novel predictors of prognosis in heart failure. *JACC Heart Fail* 3 (8), 618–625. doi:10.1016/j.jchf.2015.03.014

Jorge, M. L., De Oliveira, V. N., Resende, N. M., Paraiso, L. F., Calixto, A., Diniz, A. L., et al. (2011). The effects of aerobic, resistance, and combined exercise on metabolic control, inflammatory markers, adipocytokines, and muscle insulin signaling in patients with type 2 diabetes mellitus. *Metabolism* 60 (9), 1244–1252. doi:10.1016/j.metabol.2011.01.006

Kanmani, S., Kwon, M., Shin, M. K., and Kim, M. K. (2019). Association of C-reactive protein with risk of developing type 2 diabetes mellitus, and role of obesity and hypertension: a large population-based Korean cohort study. *Sci. Rep.* 9 (1), 4573. doi:10.1038/s41598-019-40987-8

Kasapis, C., and Thompson, P. D. (2005). The effects of physical activity on serum C-reactive protein and inflammatory markers: a systematic review. *J. Am. Coll. Cardiol.* 45 (10), 1563–1569. doi:10.1016/j.jacc.2004.12.077

Khan, M. a.B., Hashim, M. J., King, J. K., Govender, R. D., Mustafa, H., and Al Kaabi, J. (2020). Epidemiology of type 2 diabetes - global burden of disease and forecasted trends. *J. Epidemiol. Glob. Health* 10 (1), 107–111. doi:10.2991/jegh.k.191028.001

Kriketos, A. D., Greenfield, J. R., Peake, P. W., Furler, S. M., Denyer, G. S., Charlesworth, J. A., et al. (2004). Inflammation, insulin resistance, and adiposity: a study of first-degree relatives of type 2 diabetic subjects. *Diabetes Care* 27 (8), 2033–2040. doi:10.2337/diacare.27.8.2033

Lee, C. C., Adler, A. I., Sandhu, M. S., Sharp, S. J., Forouhi, N. G., Erqou, S., et al. (2009). Association of C-reactive protein with type 2 diabetes: prospective analysis and meta-analysis. *Diabetologia* 52 (6), 1040–1047. doi:10.1007/s00125-009-1338-3

Matsumori, A. (2022). Novel biomarkers of inflammation for the management of diabetes: immunoglobulin-free light chains. *Biomedicines* 10 (3), 666. doi:10.3390/biomedicines10030666

Matsumori, A., Shimada, T., Shimada, M., and Drayson, M. T. (2020). Immunoglobulin free light chains: an inflammatory biomarker of diabetes. *Inflamm. Res.* 69 (8), 715–718. doi:10.1007/s00011-020-01357-7

Nakanishi, S., Yamane, K., Kamei, N., Okubo, M., and Kohno, N. (2003). Elevated C-reactive protein is a risk factor for the development of type 2 diabetes in Japanese Americans. *Diabetes Care* 26 (10), 2754–2757. doi:10.2337/diacare.26.10.2754

Nakano, T., Matsui, M., Inoue, I., Awata, T., Katayama, S., and Murakoshi, T. (2011). Free immunoglobulin light chain: its biology and implications in diseases. *Clin. Chim. Acta* 412 (11-12), 843–849. doi:10.1016/j.cca.2011.03.007

Pedersen, B. K. (2017). Anti-inflammatory effects of exercise: role in diabetes and cardiovascular disease. *Eur. J. Clin. Invest.* 47 (8), 600–611. doi:10.1111/eci.12781

Rowley, W. R., Bezold, C., Arikan, Y., Byrne, E., and Krohe, S. (2017). Diabetes 2030: insights from yesterday, today, and future trends. *Popul. Health Manag.* 20 (1), 6–12. doi:10.1089/pop.2015.0181

Sigal, R. J., Kenny, G. P., Wasserman, D. H., Castaneda-Sceppa, C., and White, R. D. (2006). Physical activity/exercise and type 2 diabetes: a consensus statement from the American Diabetes Association. *Diabetes Care* 29 (6), 1433–1438. doi:10.2337/dc06-9910

Sparks, L. M., Johannsen, N. M., Church, T. S., Earnest, C. P., Moonen-Kornips, E., Moro, C., et al. (2013). Nine months of combined training improves *ex vivo* skeletal muscle metabolism in individuals with type 2 diabetes. *J. Clin. Endocrinol. Metab.* 98 (4), 1694–1702. doi:10.1210/jc.2012-3874

Stanimirovic, J., Radovanovic, J., Banjac, K., Obradovic, M., Essack, M., Zafirovic, S., et al. (2022). Role of C-reactive protein in diabetic inflammation. *Mediat. Inflamm.* 2022, 3706508. doi:10.1155/2022/3706508

Swift, D. L., Johannsen, N. M., Earnest, C. P., Blair, S. N., and Church, T. S. (2012). Effect of exercise training modality on C-reactive protein in type 2 diabetes. *Med. Sci. Sports Exerc* 44 (6), 1028–1034. doi:10.1249/MSS.0b013e31824526cc

Tsalamandris, S., Antonopoulos, A. S., Oikonomou, E., Papamikroulis, G. A., Vogiatzi, G., Papaioannou, S., et al. (2019). The role of inflammation in diabetes: current concepts and future perspectives. *Eur. Cardiol.* 14 (1), 50–59. doi:10.15420/ecr.2018.33.1

Van Greevenbroek, M. M., Schalkwijk, C. G., and Stehouwer, C. D. (2013). Obesity-associated low-grade inflammation in type 2 diabetes mellitus: causes and consequences. *Neth J. Med.* 71 (4), 174–187.

Wang, X., Bao, W., Liu, J., Ouyang, Y. Y., Wang, D., Rong, S., et al. (2013). Inflammatory markers and risk of type 2 diabetes: a systematic review and meta-analysis. *Diabetes Care* 36 (1), 166–175. doi:10.2337/dc12-0702

You, T., and Nicklas, B. J. (2006). Chronic inflammation: role of adipose tissue and modulation by weight loss. *Curr. Diabetes Rev.* 2 (1), 29–37. doi:10.2174/157339906775473626

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Effect of sustained decreases in sedentary time and increases in physical activity on liver enzymes and indices in type 2 diabetes

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Background: Current guidelines for nonalcoholic fatty liver disease (NAFLD) recommend high volumes and/or intensities of physical activity (PA), the achievement of which generally requires participation in supervised exercise training programs that however are difficult to implement in routine clinical practice. Conversely, counselling interventions may be more suitable, but result in only modest increases in moderate-to-vigorous-intensity PA (MVPA). This study assessed whether a counseling intervention for increasing PA and decreasing sedentary time (SED-time) is effective in improving NAFLD markers in people with type 2 diabetes.

Methods: Three-hundred physically inactive and sedentary patients were randomized 1:1 to receive one-month theoretical and practical counseling once-a-year (intervention group) or standard care (control group) for 3 years. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), and γ-glutamyltranspeptidase (γGT) levels were measured and fatty liver index (FLI), hepatic steatosis index (HSI), and visceral adiposity index (VAI) were calculated. Total PA volume, light-intensity PA (LPA), moderate-to-vigorous-intensity PA (MVPA), and SED-time were objectively measured by an accelerometer.

Results: Throughout the 3-year period, NAFLD markers did not change in the control group, whereas ALT, γGT, FLI, and HSI decreased in the intervention group, with significant between-group differences, despite modest MVPA increases, which however were associated with larger decrements in SED-time and reciprocal increments in LPA. Mean changes in NAFLD markers varied according to quartiles of (and correlated with) changes in MVPA (all markers)

and SED-time, LPA, and PA volume (ALT, γGT, and HSI). Mean changes in MVPA or PA volume were independent predictors of changes in NAFLD markers. When included in the models, change in cardiorespiratory fitness and lower body muscle strength were independently associated with some NAFLD markers.

Conclusion: A behavior change involving all domains of PA lifestyle, even if insufficient to achieve the recommended MVPA target, may provide beneficial effects on NAFLD markers in people with type 2 diabetes.

KEYWORDS

type 2 diabetes, nonalcoholic fatty liver disease, liver enzymes, physical activity, sedentary behavior

1 Introduction

Nonalcoholic fatty liver disease (NAFLD) encompasses a broad spectrum of hepatic abnormalities, from simple steatosis to nonalcoholic steatohepatitis (NASH) and cirrhosis (1), and is associated with an increased risk of developing hepatocellular carcinoma (2) and extrahepatic disorders such as cardiovascular disease (3). During the last decades, NAFLD has become the most common chronic liver disease worldwide, due to the ongoing epidemics of obesity and type 2 diabetes (4). Both these conditions are strongly associated with (5, 6) and accelerate progression of (7) NAFLD, which is in fact considered as the hepatic expression of the metabolic syndrome (8). For this reason, an international panel of experts has recently proposed to use the term metabolic dysfunction-associated fatty liver disease instead of NAFLD (9).

Current guidelines recommend, in persons with excess adiposity, a weight loss at least 5% and preferably ≥10% through an energy deficit of 500-1000 kcal with adoption of healthy eating patterns and adherence to physical activity (PA) (10–12). Regarding PA, it is advised to participate in a structured exercise program consisting of 3-5 sessions per week (10, 11), with a total duration of 150-300 min of moderate-intensity or, better, 75-150 min of vigorous-intensity aerobic exercise and eventual addition of resistance exercise training (12). Recommendations on PA are based on the evidence from studies (13–16) and meta-analyses (17–20) that engagement in aerobic and/or resistance exercise programs, generally supervised, is associated with beneficial effects on NAFLD/NASH, with significant decreases in intrahepatic fat accumulation as well as in liver enzymes and indices of steatosis and visceral adiposity. Of note, these effects were independent of weight loss (13–20), though losing weight was associated with greater benefits (18, 21, 22) with a dose-response relationship (23). Moreover, these studies were conducted either in the general population or in people with overweight/obesity and/or NAFLD/NASH, which eventually included individuals with type 2 diabetes.

Unfortunately, adherence to PA recommendation is generally poor (24), especially in people with type 2 diabetes (25), pointing to the need for targeted interventions. However, supervised exercise programs, though very effective in favoring the achievement of the high volumes and/or intensities recommended by guidelines (26), are difficult to implement in routine clinical practice. In contrast, counselling interventions may be more suitable for producing a sustained behavior change, but result in only modest increases in moderate-to-vigorous-intensity PA (MVPA) (27–29), which may be insufficient to improve NAFLD. However, sedentary time (SED-time) was found to be associated with NAFLD, independently of MVPA (30, 31), thus suggesting that targeting also this domain of PA behavior by recommending substitution or interruption with time spent in light-intensity PA (LPA) might be effective in ameliorating NAFLD. In the Italian Diabetes and Exercise Study_2 (IDES_2), a counseling intervention targeting both MVPA and SED-time resulted in only modest increases in MVPA (6.4 min·day-1), but larger (0.8 hours·day-1) decreases in SED-time and reciprocal increases in LPA, thus substantially contributing to the 3.3 metabolic equivalents (METs)-hour·week-1 increment in total PA volume (32). These changes were associated with clinically meaningful improvements in physical fitness and glycemic and blood pressure control, with no significant effect on indices of adiposity or lipid profile (32).

This *post hoc* analysis of the IDES_2 was aimed at evaluating the impact of the counseling intervention and the relative contribution of changes in MVPA and SED-time/LPA on NAFLD markers in people with type 2 diabetes.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BP, blood pressure; CON, control; FLI, fatty liver index; GLP-1 RAs, glucagon-like peptide-1 receptor agonists; γGT, γ-glutamyltranspeptidase; HSI, hepatic steatosis index; IDES_2, Italian Diabetes and Exercise Study_2; INT, intervention; LPA, light-intensity physical activity; METs, metabolic equivalents; MVPA, moderate-to-vigorous-intensity physical activity; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; PA, physical activity; SED-time, sedentary time; TDZs, thiazolidinediones; VAI, visceral adiposity index; VO_{2max}, maximal oxygen uptake.

2 Materials and methods

Design and methods have been detailed elsewhere (32, 33) and will be briefly reported here.

2.1 Design

The IDES_2 was an open-label, assessor-blinded, parallel, superiority randomized clinical trial that assessed the efficacy of a behavioral intervention in increasing daily PA and reducing SED-time over a 3-year follow-up in individuals with type 2 diabetes.

2.2 Participants

Inclusion criteria were type 2 diabetes of at least one-year duration, age 40-80 years, body mass index (BMI) 27-40 kg/m^2, physically inactivity (i.e., insufficient amounts of PA according to current guidelines) and sedentary lifestyle (i.e., more than 8 hours/day spent in any waking behavior characterized by an energy expenditure ≤1.5 metabolic equivalents while in a sitting or reclining posture) for at least 6 months, ability to walk 1.6 Km without assistance, and eligibility after cardiologic evaluation. Exclusion criteria were conditions limiting or contraindicating PA, affect conduct of the trial, reduce lifespan, and/or affect the safety of intervention.

2.3 Randomization and blinding

Three-hundred individuals with type 2 diabetes were recruited in three tertiary referral, outpatients Diabetes Clinics in Rome and randomized 1:1 to either an intervention (INT) group, receiving theoretical and practical exercise counselling, or a control (CON) group, receiving only general physician recommendations. Randomization was stratified by center and, within each center, by age < versus ≥65 years and non-insulin versus insulin treatment, using a permuted-block randomization software.

Participants from both groups received the same treatment regimen, including dietary prescription, to achieve glycemic, lipid, blood pressure (BP), and body weight targets, according to current guidelines (34). Dietary and pharmacological treatment was adjusted at each visit using a pre-specified algorithm.

Physicians, exercise specialists, and participants were not blinded, whereas assessors of accelerometer/diary and biochemical parameters were blinded to group assignment.

2.4 Intervention

Participants in the INT group were engaged in a one-month theoretical and practical counselling, each year for three years. Specifically, the intervention consisted of one individual theoretical counselling session plus eight twice-weekly individual theoretical and practical counselling sessions.

The 30-min theoretical, individual, face-to-face counselling session was held by a diabetologist and consisted of seven steps. Each theoretical and practical counselling session was held by a certified exercise specialist. The theoretical part was aimed at improving knowledge of the effects of exercise on health, conditions contraindicating exercise, difference between habitual and occasional exercise, and essential parameters of wellness such as BP, heart rate, and blood glucose. The practical part served to instruct participants to distinguish the different types of exercise, to evaluate exercise intensity, and to monitor and correct blood glucose imbalances during and after the session.

This approach was designed to promote an increase in any kind of PA, based on individual preference, and a decrease in SED-time through a two-step behavior change, i.e. (1) decreasing SED-time by substituting and/or interrupting it with a wide range of LPAs; and (2) gradually increasing the time spent in purposeful MVPA.

2.5 Measurements

2.5.1 Liver enzymes and indices of steatosis and visceral adiposity

At baseline and every 4 months thereafter, levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and γ-glutamyltranspeptidase (γGT) were measured by the use of standard methods (VITROS 5,1 FS Chemistry System, Ortho-Clinical Diagnostics Inc, Raritan, NJ). Values of the following indices were then calculated using the formulas reported in Table 1: fatty liver index (FLI) (35) and hepatic steatosis index (HSI) (36), two validated indices of steatosis, and visceral adiposity index (VAI), a marker of visceral fat distribution and dysfunction (37) that was found to predict liver histology in individuals with NAFLD (38), though not consistently (39). The following cut-off levels for liver enzymes were used (corresponding to the upper limit of laboratory range): 34 IU/L for AST, 55 IU/L for ALT, and 78 IU/L for γGT, whereas FLI, HSI, and VAI values were considered abnormal if ≥60 (intermediate if 30-59), 36, and 1.9, respectively (36, 37, 40).

2.5.2 Physical activity and sedentary behavior

Total PA volume, time spent in LPA and MVPA, and SED-time were measured by the use of an accelerometer (MyWellness Key,

TABLE 1 Formulas for calculating indices of steatosis and visceral adiposity.

Index	Formula
FLI	exp [0.953 × ln(TG) + 0.139 × BMI + 0.718 × ln(γGT) + 0.053 x [WC] − 15.745]/(1 + exp[0.953 x ln(TG) + 0.139 × BMI + 0.718 × ln (γGT) + 0.053 * [WC] - 15.745]) x 100
HSI	8 x (ALT/AST) + BMI (+2, if female; +2, if diabetes mellitus)
VAI	Men: {WC/39.68 + [(1.88 x BMI)]} x (TG/1.03) x (1.31/HDL) Women: {WC/[36.58 + (1.89 x BMI)]} x (TG/0.81) x (1.52/HDL)

FLI = fatty liver index; TG = triglycerides; γ-GT = γ-glutamyl-transpeptidase; WC = waist circumference; BMI = body mass index; HSI = hepatic steatosis index; AST = aspartate aminotransferase; ALT = alanine aminotransferase; VAI = visceral adiposity index.

Technogym, Cesena, IT) and a daily diary for non-accelerometer recordable activities. Measurements were obtained at baseline and every 4 months thereafter for seven consecutive days, except for the initial 4 months, during which the device was worn for the entire period.

2.5.3 Physical fitness

At baseline and every year thereafter, participants were evaluated for physical fitness by assessing cardiorespiratory fitness (as maximal oxygen uptake, VO_{2max}), upper and lower body muscle strength, and flexibility by maximal treadmill exercise test, isometric test, and bending test, respectively.

2.5.4 Cardiovascular risk factors

At the same time points, the modifiable cardiovascular risk factors hemoglobin A1c, fasting plasma glucose, BMI, waist circumference, triglycerides, total, HDL, and LDL cholesterol, serum creatinine (with calculation of estimated glomerular filtration rate), albumin:creatinine ratio, high-sensitivity C-reactive protein, and systolic and diastolic BP, were measured using standard methods.

2.6 Statistical analysis

Mean changes from baseline throughout the three-year follow-up in liver enzymes and indices, PA/SED-time, physical fitness, and cardiovascular risk factors were calculated for participants who completed the study as the mean values of changes from baseline at each time point (i.e., at 4, 8, 12, 16, 20, 24, 28, 32, and 36 months). Between-group differences in mean changes in AST, ALT, γGT, FLI, HSI, and VAI were assessed by Student's t test; in addition, differences in liver enzymes and indices throughout the three-year follow-up between INT and CON participants were analyzed by generalized linear mixed models for repeated measures.

To describe the relationships of changes in liver enzymes and indices with those in PA/SED-time, irrespective of study arm, the mean values of changes in AST, ALT, γGT, FLI, HSI, and VAI were then stratified by quartiles of changes in SED-time, MVPA, LPA, and PA volume in the whole cohort and data were expressed as mean ± SD and analyzed by one-way ANOVA. Moreover, univariate correlations between changes in AST, ALT, γGT, FLI, HSI, and VAI and those in SED-time, MVPA, LPA, and PA volume were assessed by Pearson correlation coefficient. Finally, multivariable linear regression analyses with stepwise backward selection of variables were applied to assess the independent predictors of changes in liver enzymes and indices over the three-year period. Study arm, age, sex, the baseline value of the dependent variable, and changes in SED-time and MVPA were included as covariates in Model 1. Changes in LPA were substituted for changes in SED-time in Model 2, whereas changes in PA volume were substituted for changes in SED-time and MVPA in model 3, respectively. All the analyses were repeated by including in the models either changes in BMI or, alternatively, waist circumference, HbA_{1c} or VO_{2max} and lower body muscle strength. Additional analyses were run to assess the independent effect of treatment with anti-hyperglycemic agents on changes in liver enzymes and indices.

All the p-values <0.05 were considered statistically significant. Statistical analyses were performed with SPSS version 20 (SPSS Inc., Chicago, IL, USA).

3 Results

As previously reported (32), 267 participants completed the study at the final evaluation (CON=134; INT=133), whereas 33 participants (CON=16; INT=17) dropped out for various reasons; of those in the INT group, >90% attended the counselling sessions.

The baseline features of the individuals considered for the present analysis are reported in Table 2.

3.1 Effects of intervention on liver enzymes and indices

No between-group differences were detected at baseline either in liver enzymes and indices or in the parameters used for calculating them (Table 2). The percentages of participants with

TABLE 2 Baseline clinical features of all participants who completed the study and by arm.

Parameter	All	CON	INT	*P*
Age, years	62.2 ± 9.7	62.7 ± 10.0	61.7 ± 9.5	0.378
Sex, n (%)				0.861
Males	162 (60.7)	82 (61.2)	80 (60.2)	
Females	105 (39.3)	52 (38.8)	53 (39.8)	
Smoking, n (%)				0.505
Never	110 (41.2)	55 (41.0)	55 (41.4)	
Former	110 (41.2)	52 (38.8)	58 (43.6)	
Current	47 (17.6)	27 (20.1)	20 (15.0)	

(Continued)

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TABLE 2 Continued

Parameter	All	CON	INT	*P*
Diabetes duration, years	10.8 ± 8.2	11.0 ± 7.9	10.6 ± 8.4	0.692
HBA_{1c}, %	7.4 ± 1.5	7.3 ± 1.4	7.4 ± 1.5	0.548
FPG, $mmol \cdot l^{-1}$	7.51 ± 2.57	7.5 ± 2.6	7.5	2.5 ± 0.859
BMI, $kg \cdot m^2$	29.9 ± 5.2	30.1 ± 5.6	29.5 ± 4.9	0.303
Waist circumference, cm	103.4 ± 12.9	103.9 ± 12.7	102.9 ± 13.1	0.529
Triglycerides, $mmol \cdot l^{-1}$	1.79 ± 1.41	1.83 ± 1.77	1.75 ± 0.92	0.663
Total cholesterol, $mmol \cdot l^{-1}$	4.66 ± 0.98	4.67 ± 1.01	4.66 ± 0.96	0.962
HDL cholesterol, $mmol \cdot l^{-1}$	1.23 ± 0.35	1.21 ± 0.35	1.25 ± 0.36	0.373
LDL cholesterol, $mmol \cdot l^{-1}$	2.90 ± 0.86	2.91 ± 0.88	2.89 ± 0.84	0.883
Systolic BP, mmHg	140.4 ± 20.8	141.3 ± 21.6	139.5 ± 19.9	0.498
Diastolic BP, mmHg	82.8 ± 11.9	83.4 ± 13.6	82.1 ± 10.0	0.366
eGFR, $ml \cdot min^{-1} \cdot 1.73\ m^{-2}$	86.8 ± 18.6	86.3 ± 18.7	87.4 ± 18.6	0.645
ACR, $mg \cdot g^{-1}$	70.2 ± 345.1	47.8 ± 125.3	92.8 ± 472.4	0.288
hs-CRP, $mg \cdot l^{-1}$	4.92 ± 8.99	5.01 ± 9.08	4.84 ± 8.93	0.878
CHD 10-year risk, %,	20.9 ± 13.7	21.8 ± 14.7	19.9 ± 12.5	0.264
Fatal CHD 10-year risk, %	15.3 ± 12.7	16.2 ± 13.7	14.5 ± 11.5	0.292
Stroke 10-year risk, %	13.8 ± 12.6	14.6 ± 12.5	13.1 ± 12.6	0.340
Fatal stroke 10-year risk, %	2.27 ± 2.47	2.43 ± 2.58	2.10 ± 2.36	0.265
AST, $UI \cdot L^{-1}$	27.1 ± 7.6	26.8 ± 7.0	27.3 ± 8.1	0.605
ALT, $UI \cdot L^{-1}$	36.6 ± 13.0	36.3 ± 13.1	37.0 ± 12.9	0.659
γGT, $UI \cdot L^{-1}$	33.7 ± 20.7	33.8 ± 21.8	33.7 ± 19.5	0.992
FLI	65.8 ± 26.4	66.3 ± 26.7	65.3 ± 26.3	0.746
HSI	42.9 ± 6.0	43.0 ± 6.3	42.8 ± 5.7	0.758
VAI	2.98 ± 2.63	3.10 ± 3.14	2.87 ± 2.00	0.471
VO_{2max}, $ml \cdot min^{-1} \cdot kg^{-1}$	24.7 ± 6.8	24.7 ± 7.3	24.7 ± 6.3	0.947
Upper body muscle strength, Nm	248.9 ± 90.1	250.9 ± 97.0	246.8 ± 82.8	0.712
Lower body muscle strength, Nm	158.9 ± 59.6	157.5 ± 59.7	160.3 ± 59.6	0.704
Bending, cm	17.0 ± 11.5	18.0 ± 12.2	16.0 ± 10.8	0.158
SED-time, $h \cdot day^{-1}$	11.6 ± 1.2	10.6 ± 4.9	11.6 ± 4.6	0.081
MVPA, $min \cdot day^{-1}$	12.5 ± 4.7	9.3 ± 4.3	10.1 ± 4.1	0.104
LPA, $h \cdot day^{-1}$	3.92 ± 1.36	1.34 ± 0.81	1.52 ± 0.76	0.058
PA volume, $METs\text{-}hour \cdot week^{-1}$	11.1 ± 4.8	11.6 ± 1.1	11.5 ± 1.2	0.456

CON, control group; INT, intervention group; HBA_{1c}, hemoglobin A_{1c}; FPG, fasting plasma glucose; BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; ACR, albumin:creatinine ratio; hs-CRP, high-sensitivity C reactive protein; CHD, coronary heart disease; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GT, γ-glutamyl-transpeptidase; FLI, fatty liver index; HSI, hepatic steatosis index; VAI, visceral adiposity index; VO_{2max}, maximal oxygen uptake; MVPA, moderate-to-vigorous-intensity physical activity; SED-time, sedentary time; LPA, light-intensity physical activity; PA, physical activity; METs, metabolic equivalents.

elevated liver enzymes were low (2.6% for AST, 7.9% for ALT, and 4.9% for γGT), whereas the percentages of those with abnormal indices were high (86.9% for FLI, of whom 26.2% with intermediate values, 89.1% for HSI, and 59.9% for VAI), with no significant differences between the two groups.

Mean changes in liver enzymes and indices were negligible in the CON group, whereas those in the INT group indicated substantial decreases in ALT, γGT, FLI, and HSI, but not AST and VAI, with significant between-group differences (Figure 1). The analysis of liver enzymes and indices throughout the 3-year follow-

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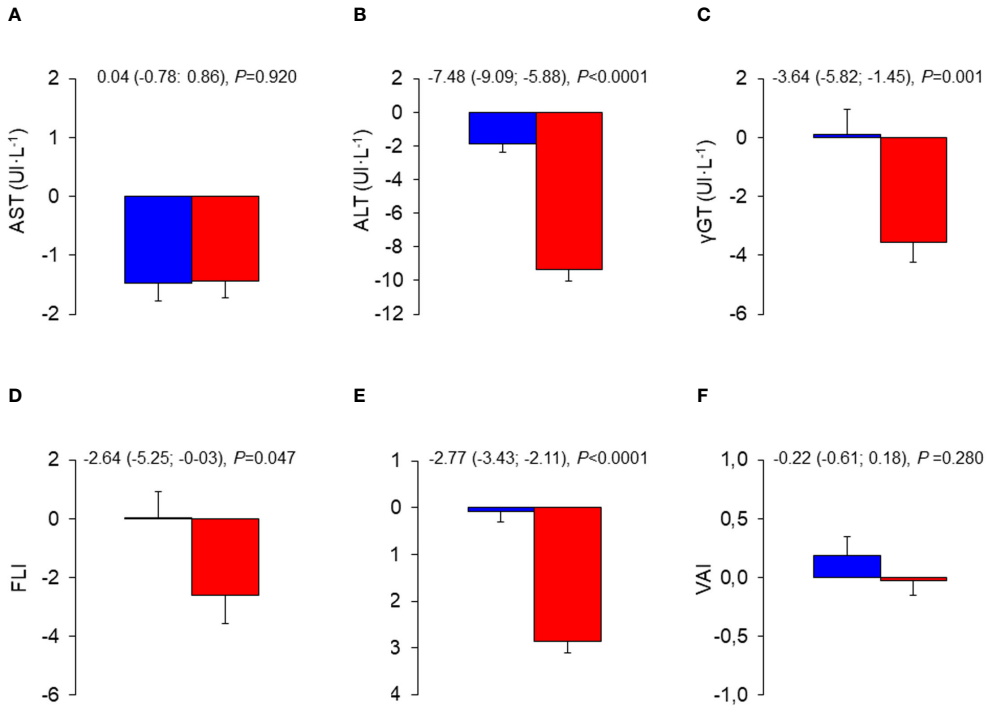

FIGURE 1
Mean changes from baseline in liver enzymes and indices in the INT and CON group. Baseline to end-of-study changes in AST **(A)**, ALT **(B)**, γ-GT **(C)**, FLI **(D)**, HSI **(E)**, and VAI **(F)** in CON (blue bars) and INT (red bars) participants. AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GT, γ-glutamyltranspeptidase; FLI, fatty liver index; HSI, hepatic steatosis index; VAI, visceral adiposity index; CON, control; INT, intervention.

up period showed no change in the CON group, and significant decreases in ALT, γGT, FLI, and HSI, but not AST and VAI, in the INT group, with significant between-group differences for ALT and HSI only (Figure 2). At end-of-study, the percentages of participants with elevated liver enzyme levels (1.6% for AST, 2,7% for ALT, and 3.5% for γGT) and abnormal indices (84.3% for FLI, of whom 24.7% with intermediate values, and 82.4% for HSI) were lower than at baseline, except for VAI (64.9%). In the CON group, the individuals that became abnormal were more numerous than those that returned normal, whereas the opposite was observed in the INT group (not shown).

3.2 Relationships between changes in liver enzymes and indices and changes in PA/SED-time and fitness

Mean changes from baseline in liver enzymes and indices significantly varied according to quartiles of changes in MVPA, with participants falling in quartiles III and IV showing the most marked reductions in these parameters. The same trend was observed according to quartiles of changes in SED-time, LPA, and PA volume, though only for ALT, γGT, and HSI (Table 3).

Likewise, at univariate analysis (Table 4), mean changes from baseline in ALT, γGT, and HSI significantly correlated with mean changes in SED-time and, inversely, with those in MVPA, LPA, and total PA volume, whereas changes in FLI and VAI correlated significantly only with changes in MVPA.

At multivariable linear regression analysis (Table 5), change in MVPA, but not change in SED-time (in Model 1) or LPA (in Model 2), was an independent predictor of changes in ALT, γGT, FLI, HSI, and VAI, but not AST. Removal of MVPA change from the models resulted in a significant association of change in SED-time with changes in ALT, γGT, HSI, and VAI or of change in LPA with changes in ALT and VAI (not shown). In Model 3, change in PA volume was an independent predictor of changes in the same parameters as MVPA in Model 1 and 2. In addition, study arm, age, and sex were variably associated with changes in liver enzymes and indices, whereas the baseline value of the dependent variable was significantly associated with its change over the study follow-up, except for HSI. When included in the models, change in BMI was significantly associated with changes in AST, ALT (in Model 2 only), γGT, FLI, and HSI, change in waist circumference was significantly associated with change in FLI, HSI, and VAI, and change in HbA1c was significantly associated with changes in γGT, FLI, HSI, and VAI, without substantially modifying the relationships between changes in MVPA or PA volume with changes in liver enzymes and indices (not shown). Moreover, among the antihyperglycemic agents, only glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and thiazolidinediones (TDZs), which were used in 14 CON versus 20 INT (P=0.261) and 33 CON versus 17 INT (P=0.013) participants, respectively, at any time during the 3-year period, were independently associated with changes in NAFLD markers, in particular HSI for GLP-1 RAs and VAI for both, without any significant impact on the association between changes in these indices and those in MVPA or PA

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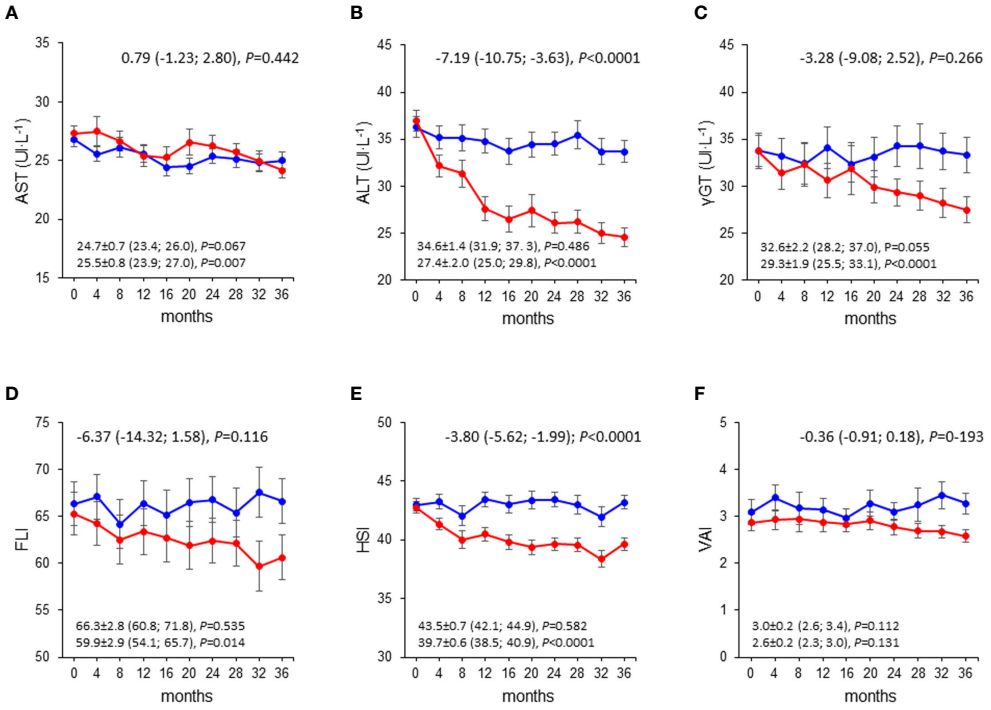

FIGURE 2
Liver enzymes and indices over the 3-year follow-up in the INT and CON group. Values of AST **(A)**, ALT **(B)**, γ-GT **(C)**, FLI **(D)**, HSI **(E)**, and VAI **(F)** over the 3-year follow-up in CON (blue circles and lines) and INT (red circles and lines) participants. AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GT, γ-glutamyltranspeptidase; FLI, fatty liver index; HSI, hepatic steatosis index; VAI, visceral adiposity index; CON, control; INT, intervention.

TABLE 3 Mean changes from baseline in liver enzymes and indices according to quartiles of mean changes from baseline in SED-time, MVPA, LPA, or PA volume.

Variables	Quartiles of mean change in SED-time *vs.* baseline				*p*
Mean change in:	I	II	III	IV	
N	67	66	68	66	
SED-time, h·day^{-1}	0.72 ± 0.39	-0.09 ± 0.17	-0.60 ± 0.18	-1.53 ± 0.43	
(range)	(1.94; 0.23)	(0.22; -0.33)	(-0.34; -0.99)	(-1.00; -3.08)	
AST, UI·L^{-1}	-1.25 ± 3.74	-2.05 ± 3.28	-1.26 ± 3.66	-1.26 ± 2.86	0.446
ALT, UI·L^{-1}	-2.22 ± 7.21	-4.03 ± 6.63	-7.19 ± 7.93	-9.04 ± 6.98	<0.0001
γGT, UI·L^{-1}	0.90 ± 10.86	-0.50 ± 8.28	-2.77 ± 8.23	-4.51 ± 8.57	0.003
FLI	-0.37 ± 9.29	-0.85 ± 12.94	-0.65 ± 9.70	-3.28 ± 11.25	0.388
HSI	-0.42 ± 2.98	-0.65 ± 3.17	-1.81 ± 2.82	-2.97 ± 2.65	<0.0001
VAI	0.37 ± 1.95	-0.08 ± 1.88	-0.06 ± 1.20	0.11 ± 1.37	0.357
Variables	Quartiles of mean change in MVPA *vs.* baseline				*p*
Mean change in:	I	II	III	IV	
N	67	67	67	66	
MVPA, min·day^{-1}	-3.33 ± 2.17	0.27 ± 0.84	4.02 ± 1.58	14.32 ± 6.59	
(range)	(-10.81; -1.09)	(-1.08; 1.87)	(1.88; 7.20)	(7.24; 34.95)	
AST, UI·L^{-1}	-1.36 ± 3.44	-1.16 ± 4.10	-2.76 ± 3.24	-0.51 ± 2.22	0.001
ALT, UI·L^{-1}	-0.99 ± 5.62	-4.05 ± 7.51	-8.99 ± 8.10	-8.49 ± 6.20	<0.0001

(Continued)

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TABLE 3 Continued

Variables	Quartiles of mean change in MVPA *vs.* baseline				*p*
Mean change in:	I	II	III	IV	
γGT, UI·L^{-1}	2.50 ± 6.64	0.57 ± 9.94	-4.07 ± 10.14	-5.94 ± 7.21	<0.0001
FLI	2.47 ± 9.48	-0.12 ± 9.56	-3.60 ± 10.90	-3.90 ± 12.30	0.001
HSI	0.36 ± 2.91	-1.08 ± 3.14	-2.18 ± 2.66	-2.97 ± 2.53	<0.0001
VAI	0.38 ± 2.01	0.32 ± 0.93	-0.42 ± 2.01	0.06 ± 1.19	0.017
Variables	Quartiles of mean change in LPA *vs.* baseline				*p*
Mean change in:	I	II	III	IV	
N	66	67	67	67	
LPA, h·day^{-1}	-0.73 ± 0.41	0.05 ± 0.15	0.55 ± 0.18	1.36 ± 0.50	
(range)	(-1.96; -0.20)	(-0.19; 0.29)	(0.31; 0.90)	(0.92; 3.70)	
AST, UI·L^{-1}	-1.91 ± 3.29	-0.92 ± 3.66	-1.55 ± 3.71	-1.43 ± 2.88	0.409
ALT, UI·L^{-1}	-2.60 ± 7.76	-4.17 ± 6.47	-6.67 ± 7.86	-8.98 ± 6.98	<0.0001
γGT, UI·L^{-1}	-0.10 ± 9.99	-0.67 ± 9.97	-1.81 ± 8.21	-4.26 ± 8.27	0.046
FLI	-0.13 ± 10.50	-0.53 ± 11.56	-2.19 ± 12.25	-2.24 ± 8.99	0.565
HSI	-0.48 ± 3.24	-0.98 ± 3.05	-1.59 ± 2.91	-2.78 ± 2.63	<0.0001
VAI	0.09 ± 2.40	0.25 ± 1.19	-0.06 ± 1.56	0.05 ± 1.09	0.740
Variables	Quartiles of mean change in PA volume *vs.* baseline				*p*
Mean change in:	I	II	III	IV	
N	66	67	67	67	
PA volume, METs·hour·week^{-1}	-1.90 ± 1.34	0.22 ± 0.34	1.85 ± 0.57	4.85 ± 1.57	
(range)	(-6.57; -0.43)	(-0.35; 0.81)	(0.90; 3.02)	(3.06; 9.14)	
AST, UI·L^{-1}	-1.45 ± 3.59	-1.62 ± 3.60	-1.70 ± 3.57	-1.04 ± 2.83	0.683
ALT, UI·L^{-1}	-1.60 ± 7.11	-4.33 ± 7.18	-7.35 ± 7.63	-9.14 ± 6.52	<0.0001
γGT, UI·L^{-1}	0.97 ± 9.44	-0.25 ± 10.34	-3.25 ± 7.95	-4.30 ± 8.20	0.002
FLI	0.25 ± 9.37	0.08 ± 11.61	-2.98 ± 13.26	-2.44 ± 8.45	0.191
HSI	-0.36 ± 3.32	-0.57 ± 2.88	-2.05 ± 2.96	-2.85 ± 2.39	<0.0001
VAI	0.16 ± 2.42	0.22 ± 1.20	-0.14 ± 1.51	0.09 ± 1.10	0.600

Values are mean ± SD, unless otherwise specified. SED-time, sedentary time; MVPA, moderate-to-vigorous-intensity physical activity; LPA, light-intensity physical activity; PA, physical activity; METs, metabolic equivalents; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GT, γ-glutamyl-transpeptidase; FLI, fatty liver index; HSI, hepatic steatosis index; VAI, visceral adiposity index.

volume. Finally, when included in the models, change in VO_{2max} was associated with changes in ALT and VAI in Model 1 and 2 and changes in ALT, γGT, and HSI in Model 3, whereas change in lower body muscle strength was an independent predictor of changes in FLI and, in Model 3 only, VAI, without substantially modifying the relationships between changes in MVPA or PA volume with changes in liver enzymes and indices (Table 6).

4 Discussion

This *post hoc* analysis of the IDES_2 showed that sustained decreases in SED-time and increases in PA promoted by a behavioral counseling were associated with improvements in NAFLD markers, with significant reductions of ALT, γGT, FLI, and HSI, whereas VAI was unchanged, consistent with the lack of effect of the intervention on indices of adiposity such as BMI and waist circumference (32). Though relatively modest, the improvements in NAFLD markers were similar to those reported in previous studies (41, 42) and meta-analyses (17, 19) for supervised exercise programs of shorter duration. In particular, in the previous IDES (42), enzyme levels did not change, whereas FLI and VAI significantly decreased in the supervised exercise intervention group, but not in the control group, in a PA volume-dependent manner.

However, participants in supervised exercise studies were engaged in moderate-to vigorous intensity training or high intensity interval training at least three times a week, thus

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TABLE 4 Univariate correlation between mean changes from baseline in liver enzymes and indices and those in SED-time, MVPA, LPA, or PA volume.

Change in:	SED-time change		MVPA change		LPA change		PA volume change	
	rho	*p*	rho	*p*	rho	*p*	rho	*p*
AST	-0.073	0.233	0.056	0.361	0.049	0.428	0.077	0.212
ALT	0.387	<0.0001	-0.519	<0.0001	-0.351	<0.0001	-0.435	<0.0001
γGT	0.309	<0.0001	-0.482	<0.0001	-0.251	<0.0001	-0.342	<0.0001
FLI	0.062	0.311	-0.212	<0.0001	-0.055	0.370	-0.088	0.152
HSI	0.367	<0.0001	-0.447	<0.0001	-0.364	<0.0001	-0.440	<0.0001
VAI	0.039	0.526	-0.139	0.023	-0.082	0.182	-0.081	0.188

SED-time, sedentary time; MVPA, moderate-to-vigorous-intensity physical activity; LPA, light-intensity physical activity; PA, physical activity; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GT, γ-glutamyl-transpeptidase; FLI, fatty liver index; HSI, hepatic steatosis index; VAI, visceral adiposity index.

TABLE 5 Independent predictors of mean changes from baseline in liver enzymes and indices.

Model 1												
Dependent variable change	AST		ALT		γGT		FLI		HSI		VAI	
	Beta	*p*	Beta	*p*	Beta	*p*	Beta	*p*	Beta	*p*	Beta	*p*
Study arm	–	–	-5.703	<0.0001	–	–	–	–	-2.160	<0.0001	–	–
Age	–	–	-0.071	0.071	–	–	-0.151	0.021	–	–	-0.014	0.090
Sex	-0.910	0.028	-1.824	0.020	–	–	-2.329	0.076	-0.761	0.023	–	–
MVPA change	–	–	-0.251	<0.0001	-0.449	<0.0001	-0.287	0.001	-0.090	<0.0001	-0.031	0.005
SED-time change	–	–	–	–	–	–	–	–	–	–	–	–
Dependent variable baseline	-0.132	<0.0001	-0.198	<0.0001	-0.134	<0.0001	-0.092	<0.0001	–	–	-0.359	<0.0001
Model 2												
Dependent variable change	AST		ALT		□GT		FLI		HSI		VAI	
	Beta	*p*	Beta	*p*	Beta	*p*	Beta	*p*	Beta	*p*	Beta	*p*
Study arm	–	–	-5.703	<0.0001	–	–	–	–	-2.160	<0.0001	–	–
Age	–	–	-0.071	0.071	–	–	-0.151	0.021	–	–	-0.014	0.090
Sex	-0.910	0.028	-1.824	0.020	–	–	-2.329	0.076	-0.761	0.023	–	–
MVPA change	–	–	-0.251	<0.0001	-0.449	<0.0001	-0.287	0.001	-0.090	<0.0001	-0.031	0.005
LPA change	–	–	–	–	–	–	–	–	–	–	–	–
Dependent variable baseline	-0.132	<0.0001	-0.198	<0.0001	-0.134	<0.0001	-0.092	<0.0001	–	–	-0.359	<0.0001
Model 3												
Dependent variable change	AST		ALT		□GT		FLI		HSI		VAI	
	Beta	*p*	Beta	*p*	Beta	*p*	Beta	*p*	Beta	*p*	Beta	*p*
Study arm	–	–	-6.085	<0.0001	–	–	–	–	-2.383	<0.0001	–	–
Age	–	–	-0.072	0.070	–	–	-0.156	0.019	–	–	-0.015	0.066
Sex	-0.910	0.028	-1.689	0.033	–	–	-2.285	0.085	-0.728	0.033	–	–
PA volume change	–	–	-0.512	0.002	-0.891	<0.0001	-0.581	0.015	-0.148	0.037	-0.102	0.001
Dependent variable baseline	-0.132	<0.0001	-0.186	<0.0001	-0.133	<0.0001	-0.086	<0.0001	–	–	-0.362	<0.0001

AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GT, γ-glutamyl-transpeptidase; FLI, fatty liver index; HSI, hepatic steatosis index; VAI, visceral adiposity index; BMI, body mass index; MVPA, moderate-to-vigorous-intensity physical activity; SED-time, sedentary time; LPA, light-intensity physical activity; PA, physical activity.

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TABLE 6 Independent predictors of mean changes from baseline in liver enzymes and indices.

Model 1												
Dependent variable change	AST		ALT		γGT		FLI		HSI		VAI	
	Beta	*p*	Beta	*p*	Beta	*p*	Beta	*p*	Beta	*p*	Beta	*p*
Study arm	–	–	-5.087	<0.0001	–	–	–	–	-2.053	<0.0001	–	–
Age	–	–	-0.068	0.083	–	–	-0.168	0.011	–	–	-0.016	0.065
Sex	-0.963	0.019	-2.100	0.008	–	–	-2.462	0.060	-0.699	0.038	–	–
MVPA change	–	–	-0.194	0.003	-0.459	<0.0001	-0.187	0.043	-0.098	<0.0001	–	–
SED-time change	–	–	–	–	–	–	–	–	–	–	–	–
VO_{2max} change	–	–	-0.296	0.017	–	–	–	–	–	–	-0.056	0.025
Lower body strength change	–	–	–	–	–	–	-0.065	0.006	–	–	-0.006	0.069
Dependent variable baseline	-0.138	<0.0001	-0.201	<0.0001	-0.132	<0.0001	-0.094	<0.0001	–	–	-0.361	<0.0001
Model 2												
Dependent variable change	AST		ALT		☒GT		FLI		HSI		VAI	
	Beta	*p*	Beta	*p*	Beta	*p*	Beta	*p*	Beta	*p*	Beta	*p*
Study arm	–	–	-5.087	<0.0001	–	–	–	–	-2.053	<0.0001	–	–
Age	–	–	-0.068	0.083	–	–	-0.168	0.011	–	–	-0.016	0.065
Sex	-0.963	0.019	-2.100	0.008	–	–	-2.462	0.060	-0.699	0.038	–	–
MVPA change	–	–	-0.194	0.003	-0.459	<0.0001	-0.187	0.043	-0.098	<0.0001	–	–
LPA change	–	–	–	–	–	–	–	–	–	–	–	–
VO_{2max} change	–	–	-0.296	0.017	–	–	–	–	–	–	-0.056	0.025
Lower body strength change	–	–	–	–	–	–	-0.065	0.006	–	–	-0.006	0.069
Dependent variable baseline	-0.138	<0.0001	-0.201	<0.0001	-0.132	<0.0001	-0.094	<0.0001	–	–	-0.361	<0.0001
Model 3												
Dependent variable change	AST		ALT		☒GT		FLI		HSI		VAI	
	Beta	*p*	Beta	*p*	Beta	*p*	Beta	*p*	Beta	*p*	Beta	*p*
Study arm	–	–	-5.915	<0.0001	–	–	–	–	-2.348	<0.0001	–	–
Age	–	–	-0.067	0.092	–	–	-0.166	0.013	–	–	-0.017	0.045
Sex	-0.963	0.019	-2.100	0.009	–	–	-2.624	0.047	-0.742	0.031	–	–
PA volume change	–	–	–	–	-0.527	0.025	–	–	–	–	-0.077	0.021
VO_{2max} change	–	–	-0.477	<0.0001	-0.469	0.005	-0.337	0.084	-0.136	0.005	–	–
Lower body strength change	–	–	–	–	–	–	-0.062	0.013	–	–	-0.007	0.025
Dependent variable baseline	-0.138	<0.0001	-0.199	<0.0001	-0.129	<0.0001	-0.093	<0.0001	–	–	-0.365	<0.0001

AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GT, γ-glutamyl-transpeptidase; FLI, fatty liver index; HSI, hepatic steatosis index; VAI, visceral adiposity index; MVPA, moderate-to-vigorous-intensity physical activity; SED-time, sedentary time; LPA, light-intensity physical activity; PA, physical activity.

accumulating large amounts of MVPA, which were shown to be required for obtaining significant decreases in intrahepatic fat accumulation (43). Conversely, in the IDES_2, increments in MVPA were much lower, though sustained over three years, and not sufficient to achieve the recommended target of at least 150-300 min per week. Thus, the novel information provided by our study is that even small increments in MVPA obtained by adopting and maintaining a more active lifestyle can be effective in improving NAFLD markers in individuals with type 2 diabetes, suggesting that "some (MVPA) is better than nothing". Yet, the findings that participants falling in quartiles III and IV of MVPA change showed the most marked reductions in liver enzymes and indices and that the increase in MVPA was a strong independent predictor of improvements in NAFLD markers confirm the concept that "the more (MVPA) the better".

Moreover, the modest changes in MVPA were accompanied by larger decrements in SED-time and reciprocal increments in LPA resulting in substantial increases in total PA volume. These changes

were also associated with changes in liver enzymes and indices, consistent with previous evidence that sedentary behavior or, inversely, overall PA level are associated with presence of NAFLD or increased liver enzymes (30, 31, 44, 45). These findings suggest that NAFLD may also benefit from reallocation of SED-time to LPA. In fact, though changes in SED-time or LPA were not independent predictors of variations in NAFLD markers, a role for decreases in SED-time through the reciprocal increases in LPA is supported by the independent association of liver enzymes and indices with total PA volume, of which increments in LPA were a main contributor.

Another important finding of this study is that changes in VO_{2max} and lower body muscle strength predicted changes in NAFLD markers beyond changes in PA/SED-time, thus suggesting that the improvements in physical fitness resulting from the behavioral modification provided additional benefits. This is consistent with the observations that cardiorespiratory fitness is associated with presence of NAFLD, as assessed by FLI, independent of MVPA (46), and that baseline VO_{2max} is an independent predictor of reduction in liver fat from a lifestyle intervention in individuals with NAFLD (47). Moreover, changes in BMI and, to a lesser extent, waist circumference were also associated, independent of changes in PA/SED-time, with changes in NAFLD markers, including the indices calculated using these parameters.

Several mechanisms have been hypothesized for explaining the beneficial effects on NAFLD of increasing PA and physical fitness and decreasing SED-time in the absence of significant reductions in total and central fat mass. These mechanisms include amelioration of insulin resistance at both the liver and adipose tissue level and increased mitochondrial biogenesis and capillarization favoring fatty acid uptake, β-oxidation, and triglyceride storage at the muscle level (48). The importance of muscle in the pathogenesis of NAFLD is supported by the inverse association of muscle mass and grip strength with risk of severe NAFLD (49) and the correlation between muscle fat accumulation and NASH severity (50). These mechanisms might be operating also for modest increases in MVPA, provided that they are sustained in the long-term.

The main strength of this study is the evaluation of changes in liver enzymes and indices of steatosis associated with long-term, sustained changes in PA/SED-time, as measured objectively by the use of an accelerometer. Other strengths concern the trial design, including the application of an intervention targeting both PA and SED-time, based on solid theoretical grounds, and using several behavioral change techniques, the specific training of investigators, the long study duration, and the large sample size (32, 33). However, this study has some limitations. First, the use of surrogate measures, such as liver enzymes and indices of steatosis, instead of direct methods, such as the gold standard histology or imaging techniques, does not allow to draw definite conclusions regarding the effect of the intervention on NAFLD/NASH. Second, the lack of data on platelet count did not allow calculation of indices of liver fibrosis. Third, generalization requires further investigation and validation in different cohorts or settings. Fourth, results might have been affected by unmeasured confounders, for instance diet, which was not considered in data analysis, though participants received dietary prescriptions and adherence to diet was verified at intermediate visits.

5 Conclusion

This *post hoc* analysis of the IDES_2 showed that, in individuals with type 2 diabetes, a counseling intervention for increasing PA and decreasing SED-time was effective in ameliorating NAFLD, as suggested by the improvements in liver enzymes and indices of steatosis over 3 years. Changes in MVPA, though modest, were the main predictors of changes in these surrogate measures, but also the greater decreases in SED-time contributed to this effect, possibly through the reciprocal increases in LPA that resulted in a relatively large increment in total PA volume. These findings indicate that a behavior change involving all domains of PA lifestyle, even if insufficient to achieve the recommended MVPA target, may also provide beneficial effects on NAFLD/NASH in people with type 2 diabetes, eventually combined with treatment with GLP-1 RAs and/or TDZs.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Ethics Committee of Sant'Andrea University Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

JH: Conceptualization, Data curation, Formal analysis, Investigation, Validation, Writing – review & editing. MV: Conceptualization, Data curation, Formal analysis, Investigation, Writing – review & editing. LM: Data curation, Formal analysis, Investigation, Writing – review & editing. CG: Data curation, Formal analysis, Investigation, Writing – review & editing. MS: Investigation, Methodology, Resources, Validation, Writing – review & editing. GO: Investigation, Methodology, Resources, Validation, Writing – review & editing. CI: Investigation, Validation, Writing – review & editing. SM: Investigation, Visualization, Writing – review & editing. SZ: Investigation, Methodology, Resources, Validation, Writing – review & editing. AN: Data curation, Formal analysis, Software, Writing – review & editing. SB: Data curation, Formal analysis, Funding acquisition, Investigation, Project administration, Supervision, Writing – review & editing, Resources. GP: Conceptualization, Data curation, Formal

analysis, Investigation, Project administration, Supervision, Writing – original draft.

Group members of Italian Diabetes Exercise Study 2 (IDES_2) Investigators

See Supplementary Data Sheet 1 for a complete list of the IDES_2 Investigators.

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Conflict of interest

SZ is an employee of Technogym. AN reported grant from Artsana, Astra-Zeneca, Eli Lilly, Novo Nordisk, and Sanofi Aventis and personal fees from Eli Lilly and Novo Nordisk. SB reported personal fees from Astra-Zeneca, Eli Lilly, Novo Nordisk, and Takeda. GP reported personal fees from Astra-Zeneca, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dome, Mylan, Sigma-Tau, and Takeda.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2024.1393859/full#supplementary-material

References

1. Sheka AC, Adeyi O, Thompson J, Hameed B, Crawford PA. 2 S. Nonalcoholic steatohepatitis: A review. *JAMA*. (2020) 323:1175–83. doi: 10.1001/jama.2020.2298

2. Shah PA, Patil R, Harrison SA. NAFLD-related hepatocellular carcinoma: The growing challenge. *Hepatology*. (2023) 77:323–38. doi: 10.1002/hep.32542

3. Duell PB, Welty FK, Miller M, Chait A, Hammond G, Ahmad Z, et al. Nonalcoholic fatty liver disease and cardiovascular risk: A scientific statement from the american heart association. *Arterioscler Thromb Vasc Biol*. (2022) 42:e168–85. doi: 10.1161/ATV.0000000000000153

4. Younossi Z, Anstee QM, Marietti M, Hardy T, Henry L, Eslam M, et al. Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention. *Nat Rev Gastroenterol Hepatol*. (2018) 15:11–20. doi: 10.1038/nrgastro.2017.109

5. Quek J, Chan KE, Wong ZY, Tan C, Tan B, Lim WH, et al. Global prevalence of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in the overweight and obese population: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol*. (2023) 8:20–30. doi: 10.1016/S2468-1253(22)00317-X

6. Younossi ZM, Golabi P, de Avila L, Paik JM, Srishord M, Fukui N, et al. The global epidemiology of NAFLD and NASH in patients with type 2 diabetes: A systematic review and meta-analysis. *J Hepatol*. (2019) 71:793–801. doi: 10.1016/j.jhep.2019.06.021

7. Schuppan D, Surabattula R, Wang XY. Determinants of fibrosis progression and regression in NASH. *J Hepatol*. (2018) 68:238–50. doi: 10.1016/j.jhep.2017.11.012

8. Cariou B, Byrne CD, Loomba R, Sanyal AJ. Nonalcoholic fatty liver disease as a metabolic disease in humans: A literature review. *Diabetes Obes Metab*. (2021) 23:1069–83. doi: 10.1111/dom.14322

9. Eslam M, Sanyal AJ, George JInternational Consensus Panel. MAFLD: A consensus-driven proposed nomenclature for metabolic associated fatty liver disease. *Gastroenterology*. (2020) 158:1999–2014.e1. doi: 10.1053/j.gastro.2019.11.312

10. European Association for the Study of the Liver (EASL); European Association for the Study of Diabetes (EASD); European Association for the Study of Obesity (EASO). EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. *J Hepatol*. (2016) 64:1388–402. doi: 10.1016/j.jhep.2015.11.004

11. Cusi K, Isaacs S, Barb D, Basu R, Caprio S, Garvey WT, et al. American association of clinical endocrinology clinical practice guideline for the diagnosis and management of nonalcoholic fatty liver disease in primary care and endocrinology clinical settings: co-sponsored by the American Association for the Study of Liver Diseases (AASLD). *Endocr Pract*. (2022) 28:528–62. doi: 10.1016/j.eprac.2022.03.010

12. Younossi ZM, Corey KE, Lim JK. AGA clinical practice update on lifestyle modification using diet and exercise to achieve weight loss in the management of nonalcoholic fatty liver disease: expert review. *Gastroenterology*. (2021) 160:912–8. doi: 10.1053/j.gastro.2020.11.051

13. Keating SE, Hackett DA, Parker HM, O'Connor HT, Gerofi JA, Sainsbury A, et al. Effect of aerobic exercise training dose on liver fat and visceral adiposity. *J Hepatol*. (2015) 63:174–82. doi: 10.1016/j.jhep.2015.02.022

14. Sung KC, Ryu S, Lee JY, Kim JY, Wild SH, Byrne CD. Effect of exercise on the development of new fatty liver and the resolution of existing fatty liver. *J Hepatol*. (2016) 65:791–7. doi: 10.1016/j.jhep.2016.05.026

15. Johnson NA, Sachinwalla T, Walton DW, Smith K, Armstrong A, Thompson MW, et al. Aerobic exercise training reduces hepatic and visceral lipids in obese individuals without weight loss. *Hepatology*. (2009) 50:1105–12. doi: 10.1002/hep.23129

16. Hallsworth K, Fattakhova G, Hollingsworth KG, Thoma C, Moore S, Taylor R, et al. Resistance exercise reduces liver fat and its mediators in non-alcoholic fatty liver disease independent of weight loss. *Gut*. (2011) 60:1278–83. doi: 10.1136/gut.2011.242073

17. Babu AF, Csader S, Lok J, Gómez-Gallego C, Hanhineva K, El-Nezami H, et al. Positive effects of exercise intervention without weight loss and dietary changes in nafld-related clinical parameters: A Systematic Review and Meta-Analysis. *Nutrients*. (2021) 13:3135. doi: 10.3390/nu13093135

18. Keating SE, Hackett DA, George J, Johnson NA. Exercise and non-alcoholic fatty liver disease: a systematic review and meta-analysis. *J Hepatol*. (2012) 57:157–66. doi: 10.1016/j.jhep.2012.02.023

19. Katsagoni CN, Georgoulis M, Papatheodoridis GV, Panagiotakos DB, Kontogianni MD. Effects of lifestyle interventions on clinical characteristics of patients with non-alcoholic fatty liver disease: A meta-analysis. *Metabolism*. (2017) 68:119–32. doi: 10.1016/j.metabol.2016.12.006

20. Hashida R, Kawaguchi T, Bekki M, Omoto M, Matsuse H, Nago T, et al. Aerobic vs. resistance exercise in non-alcoholic fatty liver disease: A systematic review. *J Hepatol*. (2017) 66:142–52. doi: 10.1016/j.jhep.2016.08.023

21. Wong VW, Chan RS, Wong GL, Cheung BH, Chu WC, Yeung DK, et al. Community-based lifestyle modification programme for non-alcoholic fatty liver disease: a randomized controlled trial. *J Hepatol*. (2013) 59:536–42. doi: 10.1016/j.jhep.2013.04.013

22. Zhang HJ, He J, Pan LL, Ma ZM, Han CK, Chen CS, et al. Effects of moderate and vigorous exercise on nonalcoholic fatty liver disease: A randomized clinical trial. *JAMA Intern Med*. (2016) 176:1074–82. doi: 10.1001/jamainternmed.2016.3202

23. Koutoukidis DA, Koshiaris C, Henry JA, Noreik M, Morris E, Manoharan I, et al. The effect of the magnitude of weight loss on non-alcoholic fatty liver disease: A systematic review and meta-analysis. *Metabolism*. (2021) 115:154455. doi: 10.1016/j.metabol.2020.154455

24. Du Y, Liu B, Sun Y, Snetselaar LG, Wallace RB, Bao W. Trends in adherence to the physical activity guidelines for americans for aerobic activity and time spent on sedentary behavior among US adults, 2007 to 2016. *JAMA Netw Open*. (2019) 2:e197597. doi: 10.1001/jamanetworkopen.2019.7597

25. Mu L, Cohen AJ, Mukamal KJ. Resistance and aerobic exercise among adults with diabetes in the U. *S Diabetes Care*. (2014) 37:e175–e176. doi: 10.2337/dc14-0619

26. Umpierre D, Ribeiro PA, Kramer CK, Leitão CB, Zucatti AT, Azevedo MJ, et al. Physical activity advice only or structured exercise training and association with HbA1c levels in type 2 diabetes: a systematic review and meta-analysis. *JAMA*. (2011) 305:1790–9. doi: 10.1001/jama.2011.576

27. Harris T, Kerry SM, Limb ES, Furness C, Wahlich C, Victor CR, et al. Physical activity levels in adults and older adults 3-4 years after pedometer-based walking interventions: Long-term follow-up of participants from two randomised controlled trials in UK primary care. *PloS Med*. (2018) 15:e1002526. doi: 10.1371/journal.pmed.1002526

28. Khunti K, Griffin S, Brennan A, Dallosso H, Davies MJ, Eborall HC, et al. Promoting physical activity in a multi-ethnic population at high risk of diabetes: the 48-month PROPELS randomised controlled trial. *BMC Med*. (2021) 19:130. doi: 10.1186/s12916-021-01997-4

29. Andrews RC, Cooper AR, Montgomery AA, Norcross AJ, Peters TJ, Sharp DJ, et al. Diet or diet plus physical activity versus usual care in patients with newly diagnosed type 2 diabetes: the Early ACTID randomised controlled trial. *Lancet*. (2011) 378:129–39. doi: 10.1016/S0140-6736(11)60442-X

30. Ryu S, Chang Y, Jung HS, Yun KE, Kwon MJ, Choi Y, et al. Relationship of sitting time and physical activity with non-alcoholic fatty liver disease. *J Hepatol*. (2015) 63:1229–37. doi: 10.1016/j.jhep.2015.07.010

31. Li J, Hua S, Chen GC, Strizich G, Kuniholm MH, Shan Z, et al. Objectively measured sedentary time, physical activity and liver enzyme elevations in US Hispanics/Latinos. *Liver Int*. (2020) 40:1883–94. doi: 10.1111/liv.14514

32. Balducci S, D'Errico V, Haxhi J, Sacchetti M, Orlando G, Cardelli P, et al. Effect of a behavioral intervention strategy on sustained change in physical activity and sedentary behavior in patients with type 2 diabetes: the IDES_2 randomized clinical trial. *JAMA*. (2019) 321:880–90. doi: 10.1001/jama.2019.0922

33. Balducci S, Sacchetti M, Haxhi J, Orlando G, Zanuso S, Cardelli P, et al. The Italian Diabetes and Exercise Study 2 (IDES-2): a long-term behavioral intervention for adoption and maintenance of a physically active lifestyle. *Trials*. (2015) 16:569. doi: 10.1186/s13063-015-1088-0

34. American Diabetes Association. Standards of medical care in diabetes–2012. *Diabetes Care*. (2012) 35 Suppl 1:S11–63. doi: 10.2337/dc12-s011

35. Bedogni G, Bellentani S, Miglioli L, Masutti F, Passalacqua M, Castiglione A, et al. The Fatty Liver Index: a simple and accurate predictor of hepatic steatosis in the general population. *BMC Gastroenterol*. (2006) 6:33. doi: 10.1186/1471-230X-6-33

36. Lee JH, Kim D, Kim HJ, Lee CH, Yang JI, Kim W, et al. Hepatic steatosis index: a simple screening tool reflecting nonalcoholic fatty liver disease. *Dig Liver Dis*. (2010) 42:503–8. doi: 10.1016/j.dld.2009.08.002

37. Amato MC, Giordano C, Galia M, Criscimanna A, Vitabile S, Midiri M, et al. Visceral Adiposity Index: a reliable indicator of visceral fat function associated with cardiometabolic risk. *Diabetes Care*. (2010) 33:920–2. doi: 10.2337/dc09-1825

38. Petta S, Amato MC, Di Marco V, Cammà C, Pizzolanti G, Barcellona MR, et al. Visceral adiposity index is associated with significant fibrosis in patients with non-alcoholic fatty liver disease. *Aliment Pharmacol Ther*. (2012) 35:238–47. doi: 10.1111/j.1365-2036.2011.04929.x

39. Vongsuvanh R, George J, McLeod D, van der Poorten D. Visceral adiposity index is not a predictor of liver histology in patients with non-alcoholic fatty liver disease. *J Hepatol*. (2012) 57:392–8. doi: 10.1016/j.jhep.2012.03.013

40. Amato MC, Giordano C, Pitrone M, Galluzzo A. Cut-off points of the visceral adiposity index (VAI) identifying a visceral adipose dysfunction associated with cardiometabolic risk in a Caucasian Sicilian population. *Lipids Health Dis*. (2011) 10:183. doi: 10.1186/1476-511X-10-183

41. Nath P, Panigrahi MK, Sahu MK, Narayan J, Sahoo RK, Patra AA, et al. Effect of exercise on NAFLD and its risk factors: comparison of moderate versus low intensity exercise. *J Clin Transl Hepatol*. (2020) 8:120–6. doi: 10.14218/JCTH.2019.00012

42. Balducci S, Cardelli P, Pugliese L, D'Errico V, Haxhi J, Alessi E, et al. Volume-dependent effect of supervised exercise training on fatty liver and visceral adiposity index in subjects with type 2 diabetes The Italian Diabetes Exercise Study (IDES). *Diabetes Res Clin Pract*. (2015) 109:355–63. doi: 10.1016/j.diabres.2015.05.033

43. Vilar-Gomez E, Martinez-Perez Y, Calzadilla-Bertot L, Torres-Gonzalez A, Gra-Oramas B, Gonzalez-Fabian L, et al. Weight loss through lifestyle modification significantly reduces features of nonalcoholic steatohepatitis. *Gastroenterology*. (2015) 149:367–378.e5. doi: 10.1053/j.gastro.2015.04.005

44. Kim D, Vazquez-Montesino LM, Li AA, Cholankeril G, Ahmed A. Inadequate physical activity and sedentary behavior are independent predictors of nonalcoholic fatty liver disease. *Hepatology*. (2020) 72:1556–68. doi: 10.1002/hep.31158

45. Perseghin G, Lattuada G, De Cobelli F, Ragogna F, Ntali G, Esposito A, et al. Habitual physical activity is associated with intrahepatic fat content in humans. *Diabetes Care*. (2007) 30:683–8. doi: 10.2337/dc06-2032

46. Kerr CJ, Waterworth SP, Brodie D, Sandercock GRH, Ingle L. The associations between physical activity intensity, cardiorespiratory fitness, and non-alcoholic fatty liver disease. *J Gastroenterol Hepatol*. (2021) 36:3508–14. doi: 10.1111/jgh.15672

47. Kantartzis K, Thamer C, Peter A, Machann J, Schick F, Schraml C, et al. High cardiorespiratory fitness is an independent predictor of the reduction in liver fat during a lifestyle intervention in non-alcoholic fatty liver disease. *Gut*. (2009) 58:1281–8. doi: 10.1136/gut.2008.151977

48. Johnson NA, George J. Fitness versus fatness: moving beyond weight loss in nonalcoholic fatty liver disease. *Hepatology*. (2010) 52:370–81. doi: 10.1002/hep.23711

49. Petermann-Rocha F, Gray SR, Forrest E, Welsh P, Sattar N, Celis-Morales C, et al. Associations of muscle mass and grip strength with severe NAFLD: A prospective study of 333,295 UK Biobank participants. *J Hepatol*. (2022) 76:1021–9. doi: 10.1016/j.jhep.2022.01.010

50. Kitajima Y, Hyogo H, Sumida Y, Eguchi Y, Ono N, Kuwashiro T, et al. Severity of non-alcoholic steatohepatitis is associated with substitution of adipose tissue in skeletal muscle. *J Gastroenterol Hepatol*. (2013) 28:1507–14. doi: 10.1111/jgh.12227

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Effect of blood flow-restrictive resistance training on metabolic disorder and body composition in older adults with type 2 diabetes: a randomized controlled study

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Introduction: To explore whether blood flow-restrictive resistance exercise (BFRE) can be used as an alternative strategy to moderate-intensity resistance training (RT) to improve metabolic disorder and body composition in older adults with type 2 diabetes (T2DM).

Methods: This is a single-blind, randomized, controlled trial. Ninety-eight older adults with T2DM were randomly divided into three groups: BFRE group (n = 34), RT group (n = 31) and control group (n = 33). Two exercise groups received supervised collective training for a period of six months, each lasting 50 min, three times a week. The primary outcomes included fasting plasma glucose (FPG), Glycosylated hemoglobin (HbA1c), blood lipids, blood pressure, and body composition. The secondary outcome was muscle performance.

Results: After six months of intervention, the FPG, HbA1c, blood lipids, diastolic blood pressure, body composition, and muscle performance of the two exercise groups were significantly improved relative to the control group and baseline measurements ($P < 0.05$). There was no significant increase in lean mass between the two exercise groups compared to the control group and baseline ($p > 0.05$). There was no significant decrease in systolic blood pressure between the two exercise groups compared to the control group ($p > 0.05$), but it was significantly lower than their baseline ($P < 0.05$). There was no significant difference in all indicators between the two exercise groups at the baseline, third and sixth months of intervention ($p > 0.05$).

Discussion: BFRE can safely and effectively improve the metabolic disorder and body composition of older adults with T2DM. For elderly exercise beginners, BFRE can be used as an alternative strategy to moderate-intensity resistance training.

Clinical trial registration: https://www.chictr.org.cn/showproj.html?proj=178886, identifier ChiCTR2300074357.

KEYWORDS

blood flow-restrictive resistance exercise, type 2 diabetes, metabolic disorders, body composition, older adults

1 Introduction

The number of older adults with diabetes is increasing with the aging of society (1, 2). The aging process leads to changes in human body composition. One of the characteristics is the continuous and inevitable decline of muscle mass (3). The loss of muscle mass reduces the quality of available insulin-responsive target tissues, thus promoting insulin resistance and leading to the occurrence of diabetes (4). Increasing skeletal muscle mass helps regulate glucose use, lipid oxidation, and resting metabolic rate.

On the basis of a healthy diet, ensuring sufficient exercise is the most effective way to enhance skeletal muscle. Therefore, many guidelines (2) recommend that diabetic patients should perform a total of 150 min of moderate- to high-intensity exercise at least three days a week, including two-three days of resistance training (RT). Classic resistance training [60–80% of an individual's one-repetition maximum (1-RM)] has proven to be effective in improving the mass and strength of skeletal muscle and controlling blood glucose (5). Unfortunately, due to a sedentary lifestyle, fatigue, pain, cardiovascular and cerebrovascular diseases, as well as concerns about safety and lack of professional guidance, so that elderly diabetes patients find it difficult to tolerate and adhere to high-intensity exercise training (6). Older people are more inclined to choose exercise methods with high safety factors and low intensity. However, low-intensity exercise not only requires athletes to achieve exhaustion, but also consumes more time and has significantly poorer effects compared to high-intensity training (7). Therefore, there is an urgent need to find a relatively low-intensity exercise that is easy to accomplish, safe, and effective as an alternative strategy that can match the beneficial effects of moderate- to high-intensity exercise.

A promising exercise method to achieve this goal is blood flow-restrictive resistance exercise (BFRE), which is a new exercise method that combines distal ischemic preconditioning and low-intensity resistance training (8). The main difference from classical resistance exercise is reduced blood flow to the moving limbs (9). Numerous studies (10, 11) have shown that the skeletal muscle hypertrophy and strength enhancement effects observed in BFRE using only 20–30% 1-RM are comparable to those observed in moderate- to high-intensity resistance training (≥ 70% 1-RM) (12). Wang et al. (13) concluded that after six weeks of training with BFRE in healthy older adults, BFRE was more effective in stimulating skeletal muscle growth and improving muscle function in the elderly compared to the non-exercise control group. Therefore, they advocated the use of BFRE as a strategy to prevent age-related deterioration of skeletal muscle mass and function. Christiansen et al. (14) conducted a six-week study of exercise training in healthy men, in which one leg was trained with BFRE and the other leg without BFRE. The results indicated that the skeletal muscles of the leg trained with BFRE significantly increased glucose intake. This may be due to BFRE promoting a significant increase in muscle antioxidant function, GLUT4 abundance, and/or nitric oxide availability.

Compared to people of the same age and with normal blood glucose, older adults with T2DM experienced accelerated loss of muscle mass and strength (15), and had a higher risk of hypoglycemia, thrombosis, and cardiovascular and cerebrovascular diseases (16). The existing BFRE research is mainly aimed at people who are non-diabetic. Whether BFRE can safely and effectively control abnormal glucose and dyslipidemia by improving the body composition of older adults with T2DM remains unknown.

To address this problem, the effect of low-intensity BFRE on the abnormal metabolism of glucose and lipids was evaluated, along with improvements on human body composition in older adults with T2DM during a six-month, supervised exercise intervention. The results from BFRE and moderate-intensity resistance exercise were compared to explore whether BFRE can become an alternative strategy. The aim of this study is to provide more extensive exercise choices for older adults with T2DM, improve their life years, and provide a reference for exercise-based prevention and treatment of diabetes.

2 Materials and methods

2.1 Study design and participants

Participants were recruited from March to May 2023 at the three community health service centers in Daxiang District, Shaoyang City, Hunan Province, through medical staff referrals, physical examinations, lectures, broadcasts, and advertisements, etc. in the streets under their jurisdiction. The main inclusion criteria to meet eligibility for this study

were: 60–80 years old, diagnosed with T2DM according to WHO diagnostic criteria (17), sedentary (exercise< 1 hour per week), not using an insulin pump, HbA1c levels of 6.5–11.0%, stable weight (weight loss or increase of no more than 2 kg), stable medication within three months before registration, and those who signed informed consent and volunteered to participate. The exclusion criteria mainly included guidelines (2, 18–20) and research (16) that indicated that individuals with contraindications to exercise, cognitive impairment, use of drugs that affect body composition, or inability to complete predetermined exercise programs were not suitable for inclusion in this study. Before randomization, participants were guided by exercise rehabilitation therapists to perform an incremental load test using a power vehicle for a duration of 20 minutes. The exercise test comprehensively evaluated cardiopulmonary reserve function, reserve oxygen uptake, and metabolic equivalents to assess the safety of the participants during exercise. Personal baseline data was recorded to develop personalized exercise programs (21). After obtaining medical approval from a physical therapist and endocrinologist, all participants were assigned to different exercise groups and completed corresponding exercise programs as required, with a total intervention period of six months (24 weeks).

2.2 Ethical considerations

This study protocol was reviewed and approved for implementation by the Medical Ethics Committee of Shaoyang University in accordance with the International Ethical Guidelines for Biomedical Research Involving Human Subjects and the Declaration of Helsinki. In addition, this study is registered on the Chinese Clinical Trials Registry (Registration No.: ChiCTR2300074357). All participants voluntarily participated in the study and signed informed consent forms. Participants had the right to withdraw from the study at any time for any reason without any consequences for further treatment, and the data set is kept confidential.

2.3 Randomization and blinding

This study was a single-blind, randomized, controlled trial, in which an independent chief researcher assigned unique codes to anonymize participant information according to inclusion order. Then, participants were randomly assigned to three parallel groups based on a computer-generated numerical sequence: the control group, the resistance training group (RT), and the blood flow restrictive resistance exercise group (BFRE). The researchers responsible for each group intervention and evaluation were independent of each other, and the evaluators were blinded to each participant's group assignment.

2.4 Sample size

The necessary sample size was estimated as follows: $n = \frac{\Psi^2(\sum_{i=1}^{k} S_i^2/k)}{\sum_{i=1}^{k}((\chi_i-\chi)^2/(k-1)}$. In our pilot study, the mean and standard deviation (mean ± SD) of fasting plasma glucose (FPG) for the three groups were 8.64 ± 1.25 for the control group, 7.51 ± 1.31 for the RT group, and 8.01 ± 1.18 for the BFRE group. One – way ANOVA of $\alpha = 0.05$ (bilateral), $\beta = 0.10$, Ψ=2.55 were taken. To test whether there are significant differences among the three groups in the final data analysis, at least 31 participants were needed in each group. Therefore, the total sample size was calculated as 93. Based on a dropout rate of 20%, this required at least 38 participants per group, or a total of 114 participants.

2.5 Intervention measures

2.5.1 Diabetes education

Before the exercise intervention, all participants were invited to join different WeChat groups according to their grouping. We sent notifications and diabetes education materials to them through WeChat, and arranged for them to participate in diabetes health education classes at different times and stages, including diabetes healthy diet, exercise regularly, medication, blood glucose monitoring and regular follow-up appointments. The teaching format was online and offline blended teaching over a total of 13 hours (4 hours before the intervention, 1.5 hours per month of the intervention). All courses were administered by a diabetes-specialist nurse with 12 years of work experience. Before the end of each course, all participants were scheduled to take a test to ensure that they mastered the relevant knowledge.

2.5.2 Control group

During the study, participants were recommended to change their lifestyle according to our diabetes education content. However, supervised exercise interventions and detailed resistance training programs were not provided; participants could adhere to the advice to exercise and adjust their diet on their own or maintain their original lifestyle habits. A researcher recorded the daily exercise habits of participants through a fitness tracker or WeChat exercise mini-program, mobile health management software. Participants in the control group were invited to participate in physical examinations and face-to-face interviews before the intervention and at the third and sixth months of follow up appointments.

2.5.3 exercise intervention

The exercise intervention was conducted at the sports fields near the three community health service centers. The baseline values of the participants were measured before the exercise programs began. The first two weeks of the formal exercise intervention were for adaptation training to help participants develop exercise programs based on their individual baseline levels and familiarize themselves with the training process. Two professionally trained researchers supervised and led participants in training at each sports field to ensure standardized movements, achieve predetermined intensity, and ensure safety. After conducting a motivation survey, the exercise time was set between 7:30–8:30 in the evening. Thirty minutes before each exercise, the researchers asked the participants about their diet

and physical condition, and measured their blood glucose, blood pressure, and heart rate (HR). Both exercise groups warmed up for ten minutes before the main training session, which lasted for 30 minutes. A heart rate monitoring bracelet was used to dynamically monitor the HR of participants during exercise to maintain a moderate-intensity of exercise (40–59% HR reserve). Afterwards, they stretched and relaxed for ten minutes, for a total of 50 minutes. The exercise sessions were provided three times a week, with 24–48 hours' interval between each session, over a total of six months (24 weeks). If participants participated a total of 15 times a month, their attendance rate was considered to be 100%; if their attendance was ≥ 10 times per month (≥ 70% attendance rate), they were considered to have met the standard (22); if their attendance was less than seven times per month (< 50% attendance rate) (5), they were excluded if their attendance did not improve after encouragement and communication.

2.5.3.1 RT group

Resistance training was performed using small equipment such as barbells, dumbbells, elastic bands/ropes, and kettle bells because participants were expected to be able to learn to use small equipment at home after the study was over. Upper body exercises (shoulder press and pull down, elbow extension and flexion), hip and leg exercises (leg press, extension and flexion), and core muscle group exercises (flat-ground support, glute bridge, push-ups, sit-ups) were mainly selected for training. The initial intensity of the strength training program was low (40%–50% 1-RM) to reduce muscle soreness, avoid Valsalva movements and tendon injuries, and ensure proper weight lifting form. If the participant could fully adapt, that was, repeat 10–15 times/set with the same resistance, complete 2–4 sets, and self-rate the degree of fatigue during and after exercise to achieve 12–13 points of the Borg ratings of perceived exertion (RPE) scale, resistance can be gradually increased 5%–10% 1-RM until they can complete the moderate-intensity resistance training at a personal 60%-70% 1-RM, repeating 10–15 times/set, 60 seconds interval between sets (19, 23). Table 1 shows the detailed resistance training scheme.

2.5.3.2 BFRE group

The KAATSU Air Band (Product type: C3, USA) was tied to the most proximal end of the subject's upper or lower limb, with a tightness that could accommodate one finger. The KAATSU host was used to control the bandage to gradually apply pressure to the limb, while the laser Doppler flowmeter quantitative analyzer (SONIMAGE, product type: HS1, China) was used to test the minimum pressure required for the subject's limb to be blocked by arterial blood flow. The pressure displayed on the KAATSU host at this time was referred to as the total limb occlusion pressure (LOP). During each training session, the cuffs were tied to the most proximal ends of the subject's upper or lower limbs based on the main muscle groups trained, and blood flow was limited to 50% LOP of the individual's limbs (24). At the same time, resistance training intensity was 20–30% 1-RM. The training equipment and movements were the same as those in the ST group. The volume followed a scheme from 30 repetitions in the first set and 15 repetitions in set three. The rest periods between the sets were 30 s with the cuffs remaining inflated during rest. The blood flow restriction lasted for a total of 6.5 minutes. Then, the cuffs were completely relaxed to allow blood reperfusion, during which time two sets of core muscle group trainings were continued. There was a rest period of 30 s between sets. The total time for blood flow restriction + reperfusion training was ten minutes for each round, with three rounds in total for a total of 30 minutes. It is important to note that the applied cuff pressure should not cause pain or any obvious discomfort in the subject during training, and can be adjusted to 40–50% LOP based on the comfort of the subject (25). The goal in this study was to use pressure sufficient to induce muscle adaptation while minimizing discomfort to avoid interruptions in exercise due to subcutaneous bleeding, thrombosis, limb soreness, and other problems in the subject. Information on this regimen is shown in Table 2.

TABLE 1 Resistance training scheme.

Weeks	Intensity (% 1-RM)	Repetitions	Perceived Exertion (Rating on 6–20 RPE Scale)	Interval between sets	Frequency (times/ week)	Sets
1 (Pre-intervention)	40–50	8–12	9–11	1 minute	3	2–4
2 (Pre-intervention)	45–55	10–15	9–12			
1–2 (Intervention)	55–60	8–12	12–13			
3–4	55–60	10–15	12–13			
5–8	60–65	8–12	12–13			
9–12	60–65	10–15	12–14			
13–16	60–70	8–12	12–14			
17–24	60–70	10–15	12–14			

RPE, ratings of perceived exertion; 1-RM, one-repetition maximum.

TABLE 2 blood flow-restrictive resistance exercise training scheme.

Action	Time	Training location	Main movement
Inflation and pressurization	1 minute		Intensity: 20%–30% 1-RM. 10 minutes × 3 = 30 minutes
Repetitions: 1st set: 30 → 2nd set: 15→ 3rd set: 15 → 4th set: 15	A total restriction time = 6.5 minutes	Training on both upper or lower limbs with 40–50% LOP	
Interval between sets: 30 seconds			
Complete deflation and rest	30 seconds		
Continue resistance training without blood flow restriction	2 sets + 30 seconds rest × 2 = 2 minutes	Core muscles	

LOP, limb occlusion pressure; 1-RM, one-repetition maximum.

2.6 Outcome measures

The measurements were conducted at three time points: baseline (0 month), and in the third and sixth months of the intervention. The non-blood-test results were available at the end of the test, and the blood test results were reported the day after the blood collection. Researchers entered the three groups' measurement data into Excel spreadsheets separately and conducted double checks to ensure the accuracy of the data. The data entry personnel and data analysts were independent of each other. Identity information of the subjects was replaced with corresponding numbers, and all qualified data were scanned and encrypted for storage. The original report forms were distributed to the subjects themselves, and no one was allowed to disclose patient privacy information.

2.6.1 Baseline data

Before intervention, demographic and clinical characteristics of the subjects were investigated with structured questionnaires.

2.6.2 Primary outcomes

2.6.2.1 Measurement of FPG, HbA1c, blood lipids, and blood pressure

At three time points during the measurement, three groups of participants went to designated community health service centers for physical examination between 7:00 and 9:00 am. Venous blood samples were collected from the subjects after fasting for more than eight hours, then frozen at -80 °C. After centrifugation at 3000 rpm for 15 minutes, the serum was separated and analyzed. (1) HbA1c levels were measured using ion-exchange resin high-performance liquid chromatography by a Variant II HbA1c instrument (Bio-Rad, product type: 270–2001, USA). (2) A fully automatic biochemical analyzer instrument (Hitachi, product type: 7600, Japan) was used to measure levels of fasting plasma glucose (FPG), total cholesterol (TC), triglyceride (TG), low density lipoprotein cholesterol (LDL-C), and high density lipoprotein cholesterol (HDL-C). (3) After the subject rested for 15 minutes, an electronic blood pressure monitor (OmRon, product type: U730, China) was used to measure the blood pressure (BP), included the systolic blood pressure (SBP) and diastolic blood pressure (DBP). A medical professional instructed the subjects to straighten their arms and tie cuffs two centimeters above their elbow sockets. The tightness of the cuffs can accommodate one finger. The subject was seated with the brachial artery measurement point, blood pressure monitor, and heart position at the same level. They were kept quiet until the end of the blood pressure measurement, accurate to 1 mmHg.

2.6.2.2 Body composition

A direct, segmented, multi-frequencies bioelectrical impedance analyzer (DSM-BIA) (InBody, product type: 770, Korea) was used to estimate body composition. The instrument was equipped with eight electrode touch points on both sides of the thumb, palm, sole, and heel. Five segments of the limbs and trunk were subjected to multi-frequency current through six different impedance frequencies (1, 5, 50, 250, 500, and 1000 kHz) and three different reactance frequencies (5, 50, and 250 kHz) to estimate body composition. Before the test, the subjects were required to fast and empty their urine, not exercise, or drink excessively for 30 minutes. They were asked to remove their metal jewelry, shoes, and socks; clean their hands and feet with a cloth; stand barefoot in the center of the instrument chassis; and slightly separate their legs. The forefoot and heel were placed on the front and rear foot electrodes on the instrument chassis, respectively. The weight was automatically measured to an accuracy of 0.01 kg. After entering the correct height of the subject into the system, the subject was prompted to place their thumbs and palms on the handle electrodes, stand straight, stretch their arms away from both sides of their body, remain quiet, and maintain their posture until the end of the test. Upon completion of the test, a test report was available for the researcher to enter the subject's skeletal muscle mass (SMM), appendicular skeletal muscle mass (ASM), fat mass (FM), lean mass (LM), weight, and body mass index (BMI) into an Excel table and calculate the following indicators: fat mass index (FMI) = FM/Height^2 (kg/m^2), skeletal muscle mass index (SMI) = SMM/Height^2 (kg/m^2), appendicular skeletal muscle mass index (ASMI) = ASM/Height^2 (kg/m^2). Waist circumference and height were measured with a tape measure, accurate to 0.1 cm. Waist-to-height ratio (WHtR) was calculated based on waist circumference (cm)/height (cm); a WHtR > 0.5 indicates abdominal obesity. Obesity was evaluated based on BMI and divided into normal (18–23.9 kg/m^2), overweight (24–27.9 kg/m^2), and obese (≥ 28 kg/m^2) (2).

2.6.3 Secondary outcome

2.6.3.1 Muscle performance

(1) Grip strength test: An electronic grip strength meter (CAMRY, product type: EH101, China) was used to estimate grip strength. During the test, the patient was required to stand straight, fully extend their arms, and squeeze the handle of the dynamometer

with maximum strength for three seconds. The measurement was taken twice with both hands alternately. The maximum grip strength value was taken, accurate to 0.1 kg. (2) Five times-sit-to-stand test: The subject was instructed to always keep their arms crossed in front of their chest, stand up as quickly as possible from a 40 cm-high chair, and sit down again. The action was repeated five times and the time used was recorded, accurate to 0.01 seconds. (3) The 6-m walking speed test: The patient was instructed to walk straight at the fastest speed for a distance of 6 m, twice in total. The shortest time of the two records was taken, then the walking speed of the examinee was calculated, accurate to 0.01 m/s.

2.6.4 Quality control

All exercise interventions were carried out under the supervision of the researchers. During this period, if the researcher discovered events such as hypoglycemia, high blood pressure, illness, injury, etc., the participant would be required to immediately suspend or terminate the experiment, and given treatment measures within their ability. Afterwards, the treatment process should have been supplemented and recorded. The researchers needed to truthfully report the handling of adverse events to the chief researcher to arrange subsequent treatment and necessary compensation. If it was not suitable to go out for training in extreme weather, online live streaming, video playback, and other methods to guide participants to complete training at home was provided. All other training was conducted in a collective form. To reduce the dropout rate, the research group also took measures, such as regularly holding diabetes-control themed activities, providing free physical examinations and medical consultations, and issuing incentive gifts and bonuses.

2.7 Statistical analysis

Statistical analysis was performed using SPSS 23.0 (SPSS Inc., Chicago, IL, USA). For the comparison of baseline demographic characteristics between groups, the analysis of variance (ANOVA) or Kruskal-Wallis test was used for quantitative data, and the chi-square test was used for count data. The independent sample t-test was used to compare the attendance rates of the two control groups. The two-factor repeated measures ANOVA was used to analyze the changes in each dependent variable over time (from baseline to six months), and to analyze the interaction between time and population. In the case of non-compliance with the Mauchly's test of sphericity hypothesis, the results were analyzed using Greenhouse-Geisser correction. The Bonferroni correction was used for *post-hoc* multiple comparisons. The mean difference [95% Confidence Interval (CI)] within the group from post-measurement to baseline was represented by the mean difference. The effect sizes of repeated measurement ANOVA was expressed by partial eta-squared (η^2p, small ≥ 0.01; medium, ≥ 0.06; large ≥ 0.14). The effect sizes of mean differences between groups were expressed by Cohen's d (d; small, ≥ 0.2; medium, ≥ 0.5; large ≥ 0.8). The level of statistical significance was defined as 0.05.

3 Results

3.1 Participant demographics and clinical characteristics

As shown in Figure 1, in June 2023, 139 older adults with T2DM who received a qualification assessment were selected to meet the inclusion criteria. After six months of intervention (June 2023-December 2023), 41 participants were excluded due to non-compliance, disease, relocation, and other reasons. Therefore, a total of 98 participants completed this study, including 33 in the control group (dropout rate of 28.26%), 31 in the RT group (dropout rate of 34.04%), and 34 in the BFRE group (dropout rate of 26.09%). Their average attendance rate was ≥ 70%, with 82.37 ± 3.55% in the RT group and 81.74 ± 2.59% in the BFRE group. There was not significant difference in attendance rates between the two exercise groups ($t = 0.818$, $p = 0.416$, $df = 63$).

3.2 Baseline data

As shown in Table 3, the baseline data for each dependent variable among the three groups were consistent ($p > 0.05$). The average age of the participants was 66.19 ± 4.75 years old, with 39 males and 59 females, and an average height of 161.43 ± 8.80 cm. Among all participants, 91 (92.9%) had abdominal obesity (WHtR > 0.5), 88 (89.8%) were overweight/obese (BMI ≥ 24 kg/m^2), 69 (70.41%) used antihypertensive drugs, and 32 (32.7%) used medicine to regulate dyslipidemia. All participants had diabetes for more than two years, used hypoglycemic drugs to control blood glucose, and used them steadily for at least three months. During the intervention period, no patients changed the way they used hypoglycemic drugs, but some patients had to adjust their drug dosage due to changes in their condition. Four patients in the control group increased their dosage, while two patients in the RT group and two patients in the BFRE group needed to lower their dosage. There was no significant difference in drug adjustment among the three groups of participants ($\chi^2 = 1.047$, $p = 0.593$, $df = 2$).

3.3 Results of repeated measures analysis of variance

Tables 4–7 report the results of two-factor repeated measures of ANOVA used to compare and evaluate differences in FPG, HbA1C, BP, lipid profile, body composition, and muscle performance of the three groups. According to the Shapiro-Wilk test, all dependent variables basically obeyed normal distribution ($p > 0.05$). According to the Mauchly's sphericity test, except for HbA1c, DBP, LDL-C, and ASMI, all other dependent variables did not meet the sphericity hypothesis ($p < 0.05$). The dependent variables that did not meet the sphericity hypothesis were subject to the results of Greenhouse-Geisser correction. The Levene test showed that the variance of the

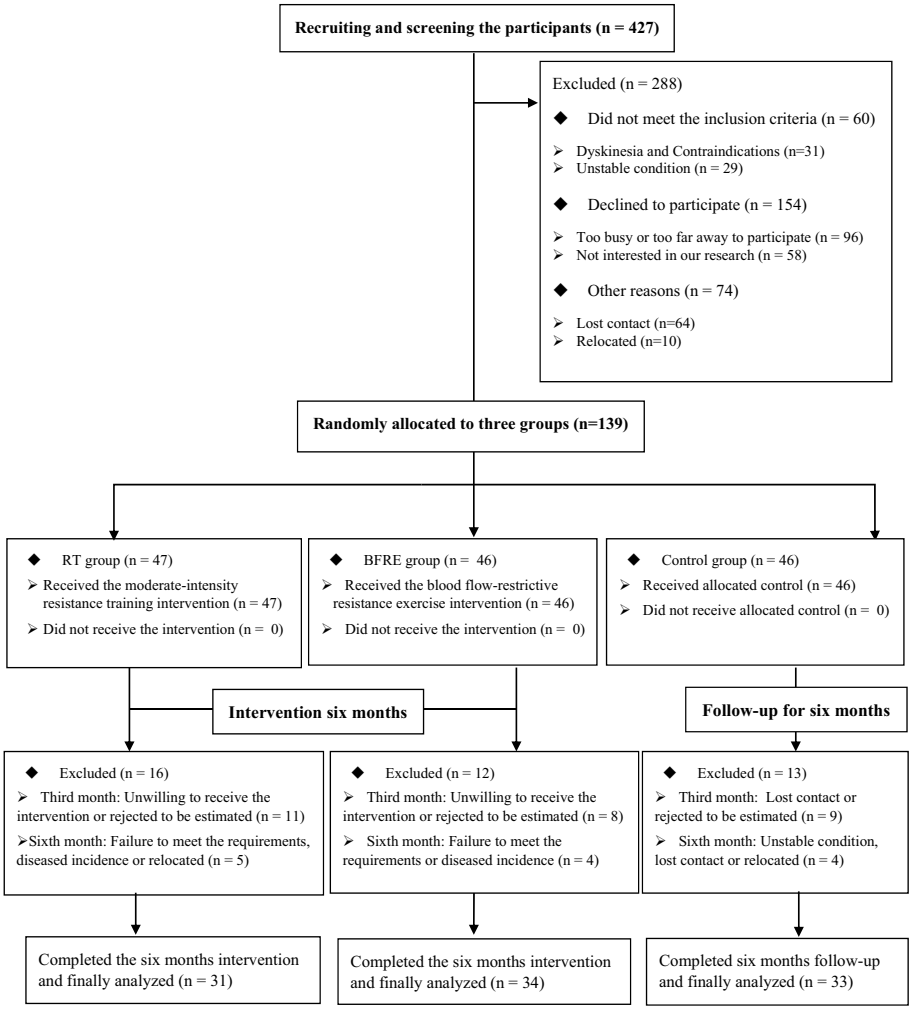

FIGURE 1
Flow chart of participant enrollment, allocation, and analysis.

dependent variables was homogeneous ($p > 0.05$). The results of repeated measures ANOVA showed that except for the (group × time) interaction effect and the main effects of group and time on lean mass, which were not significant ($p > 0.05$), as well as the main effect of group on SBP, which was not significant ($p > 0.05$), the remaining dependent variables were significantly affected by the (group × time) interaction effect, and the main effects of group and time ($p< 0.05$).

3.4 Primary outcomes

Table 4 shows the changes in FPG, HbA1c, and BP for the three groups. The results of repeated measures ANOVA indicate that the main effect of time in FPG, HbA1c, SBP and DBP were significant ($p< 0.001$). Compared to baseline, from the third month of intervention, the FPG, HbA1c, SBP and DBP of the two exercise groups decreased significantly from baseline ($p< 0.05$), and the improvement effect became more significant over time. Compared to the control group, the FPG ($d = -0.62$, $p = 0.032$) and HbA1c ($d = -0.65$, $p = 0.038$) in the RT group began to significantly decrease at the third month of intervention, while the same effect occurred in the BFRE group at the sixth month of intervention. At the sixth month of intervention, there was no significant difference in SBP between the three groups ($F = 0.915$, $p = 0.404$, $\eta^2P = 0.019$), while the FPG, HbA1c, and DBP in RT and BFRE were significantly decreased compared to the control group ($p< 0.05$), with no significant difference between the two exercise groups ($p > 0.05$).

Table 5 shows the changes in blood lipids. Compared with baseline, at the third month of intervention, TC [with a mean (95% CI) change of -0.38 (-0.72, -0.50), $p = 0.018$] and TG [-0.38, (-0.63, -0.12), $p = 0.002$] in the BFRE group decreased significantly, while

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TABLE 3 Baseline demographic and clinical characteristics for the three groups (mean ± SD/n,%).

Characteristic		Group (n=98)			F/χ^2	p
		Control (n=33)	RT (n=31)	BFRE (n=34)		
Age, years		65.55 ± 4.41	66.65 ± 4.94	66.41 ± 4.97	0.477	0.622
Height, m		162.12 ± 9.40	161.06 ± 7.92	161.38 ± 7.67	0.136	0.873
Weight, kg		70.06 ± 9.61	67.81 ± 9.70	68.79 ± 9.42	0.447	0.641
Sex	Male	14(42.4)	13(41.9)	12(35.3)	0.442	0.802
	Female	19(57.6)	18(58.1)	22(64.7)		
Medications used for dyslipidemia	Yes	11(33.3)	8(25.8)	13(38.2)	1.150	0.563
	No	22(66.7)	23(74.2)	21(61.8)		
Medications used for blood pressure	Yes	25(75.8)	21(67.7)	23(67.6)	0.683	0.711
	No	8(24.2)	10(32.3)	11(32.4)		
Course of diabetes, years	2–5	11(33.3)	13(41.9)	16(47.0)	5.896	0.207
	5–10	18(54.5)	12(38.7)	9(26.5)		
	>10	4(12.2)	6(19.4)	9(26.5)		
Glucose-lowering medication	Oral medication	22(66.7)	16(51.6)	23(67.6)	2.506	0.644
	Oral medication + insulin	7(21.2)	11(35.5)	8(23.6)		
	Other	4(12.1)	4(12.9)	3(8.8)		
Blood pressure, mmHg	Systolic	127.73 ± 10.41	128.68 ± 14.07	126.65 ± 14.38	0.196	0.822
	Diastolic	79.97 ± 7.02	78.13 ± 7.61	79.12 ± 8.19	0.446	0.629
Blood lipid components, mmol/L	TC	4.70 ± 0.87	4.54 ± 1.08	4.63 ± 0.97	0.225	0.799
	TG	2.60 ± 0.74	2.51 ± 0.82	2.46 ± 0.89	0.247	0.782
	HDL-C	1.20 ± 0.29	1.12 ± 0.32	1.21 ± 0.38	0.710	0.494
	LDL-C	2.92 ± 0.63	2.85 ± 0.52	2.74 ± 0.61	0.424	0.655
Blood glucose indicators	FPG, mmol/L	8.55 ± 1.12	8.14 ± 1.42	8.36 ± 1.46	0.761	0.470
	HbA1c,%	7.98 ± 0.96	7.80 ± 0.93	7.75 ± 0.97	0.544	0.582
Body composition	WHtR, %	0.56 ± 0.03	0.56 ± 0.04	0.55 ± 0.03	0.727	0.486
	BMI, kg/m^2	26.56 ± 1.58	26.02 ± 2.05	26.31 ± 1.88	0.675	0.512
	FM, kg	24.79 ± 3.42	22.97 ± 4.42	23.72 ± 4.60	1.540	0.220
	FMI, kg/m^2	9.49 ± 1.49	8.83 ± 1.48	9.08 ± 1.42	1.644	0.199
	Lean mass, kg	45.27 ± 8.57	44.84 ± 6.37	45.07 ± 6.70	0.028	0.972
	SMI, kg/m^2	8.79 ± 0.80	8.91 ± 0.71	8.96 ± 0.71	0.436	0.648
	ASMI, kg/m^2	6.39 ± 0.60	6.47 ± 0.55	6.54 ± 0.54	0.559	0.574
Muscle performance	Handgrip strength, kg	23.08 ± 5.18	22.94 ± 4.37	24.04 ± 5.20	0.484	0.618
	5 times sit-stand test, s	16.26 ± 3.09	15.72 ± 2.45	15.97 ± 2.47	0.323	0.725
	6-m walk test, m/s	1.08 ± 0.07	1.09 ± 0.07	1.07 ± 0.08	0.563	0.571

BFRE, blood flow-restrictive resistance exercise group; RT, moderate-intensity resistance training group; FPG, fasting plasma glucose; HbA1c, Glycosylated hemoglobin; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDLC, low-density lipoprotein cholesterol; WHtR, waist-to-height ratio; BMI, body mass index; SMM, skeletal muscle mass; ASM, appendicular skeletal muscle mass; FM, fat mass; LM, lean mass; FMI, fat mass index; SMI, skeletal muscle mass index; ASMI, appendicular skeletal muscle mass index.

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TABLE 4 Effects of interventions on FPG, HbA1c, and BP among the three groups (mean ± SD or mean difference [95% CI]).

Index and time points	Group (n=98)			Cohen's d			Repeated measurement analysis of variance			
	Control (n=33)	RT (n=31)	BFRE (n=34)	RT versus Control	BFRE versus Control	RT versus BFRE		Group × Time Interaction	Time	Group
Fasting plasma glucose (FPG), mmol/L										
T0	8.55 ± 1.12	8.14 ± 1.42	8.36 ± 1.46	−0.32	−0.15	−0.15	*F*	5.205	37.529	3.205
T3	8.48 ± 1.12	7.70 ± 1.38	7.82 ± 1.08	−0.62*	−0.6	−0.10	p	< 0.001	< 0.001	0.045
T6	8.41 ± 1.20	7.51 ± 1.13	7.63 ± 0.90	−0.77*	−0.74*	−0.12	η^2P	0.099	0.283	0.063
T3 versus T0	−0.07(−0.29,0.15)	−0.44(−0.67,−0.21)#	−0.54(−0.76,−0.32)#							
T6 versus T0	−0.15(−0.43,0.14)	−0.62(−0.91,−0.33)#	−0.73(−1.01,−0.46)#							
Glycosylated hemoglobin (HbA1c), %										
T0	7.98 ± 0.96	7.80 ± 0.93	7.75 ± 0.97	−0.19	−0.24	0.05	*F*	20.839	96.393	3.484
T3	7.95 ± 0.92	7.37 ± 0.85	7.53 ± 0.93	−0.65*	−0.45	−0.18	*p*	< 0.001	< 0.001	0.035
T6	7.93 ± 0.75	7.11 ± 0.75	7.24 ± 0.85	−1.09#	−0.86*	−0.16	η^2P	0.305	0.504	0.068
T3 versus T0	−0.04(−0.17,0.09)	−0.43(−0.56,−0.30)#	−0.22(−0.34,−0.10)#							
T6 versus T0	−0.05(−0.18,0.08)	−0.69(−0.83,−0.55)#	−0.51(−0.64,−0.38)#							
Systolic blood pressure (SBP), mmHg										
T0	127.73 ± 10.41	128.68 ± 14.07	126.65 ± 14.38	0.08	−0.09	0.14	*F*	4.589	9.897	0.915
T3	128.70 ± 13.38	125.19 ± 12.40	124.09 ± 12.43	−0.27	−0.36	0.09	*p*	0.003	< 0.001	0.404
T6	128.39 ± 10.21	124.71 ± 12.35	122.29 ± 10.85	−0.33	−0.58	0.21	η^2P	0.088	0.094	0.019
T3 versus T0	0.97(−1.55, 3.49)	−3.48(−6.08,−0.89)*	−2.56(−5.04,−0.08)*							
T6 versus T0	0.67(−2.16, 3.50)	−3.97(−6.89,−1.05)*	−4.35(−7.14,−1.56)*							
Diastolic blood pressure (DBP), mmHg										
T0	79.97 ± 7.02	78.13 ± 7.61	79.12 ± 8.19	−0.25	0.11	−0.13	*F*	8.130	8.368	3.263
T3	81.06 ± 6.81	76.23 ± 7.57	76.97 ± 9.31	−0.67	−0.5	−0.09	*p*	< 0.001	< 0.001	0.043
T6	81.42 ± 5.93	75.19 ± 7.29	75.94 ± 7.50	−0.94*	−0.81*	−0.10	η^2P	0.146	0.081	0.064
T3 versus T0	1.09(−0.61, 2.79)	−1.90(−3.66,−0.15)*	−2.15(−3.82,−0.47)*							
T6 versus T0	1.46(−2.22, 3.13)	−2.94(−4.66,−1.21)#	−3.18(−4.79,−1.56)#							

BFRE, blood flow-restrictive resistance exercise group; RT, moderate-intensity resistance training group; η^2P, partial eta-squared; T0, baseline; T3, at third month; T6, at sixth month; *, significant difference at p< 0.05; #, significant difference at p< 0.001.

HDL-C increased significantly and LDL-C decreased significantly in both exercise groups (p< 0.05). At the sixth month of intervention, TC, TG, and LDL-C decreased significantly and HDL-C increased significantly in the two exercise groups (p< 0.05), while the improvement of blood lipids in the control group were not significant (p > 0.05). Compared with the control group, at the third month of intervention, TC in both exercise groups decreased significantly [(RT, d = -0.75, p = 0.011), (BFRE, d = -0.77, p = 0.006)], and TG decreased (d = -0.75, p = 0.012) and HDL-C increased (d = 0.91, p = 0.002) significantly in the BFRE

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TABLE 5 Effects of interventions on blood lipids among the three groups [mean ± SD or mean difference (95% CI)].

Indexes and time points	Group (n=98)			Cohen's d			Repeated measurement analysis of variance			
	Control (n=33)	RT (n=31)	BFRE (n=34)	RT versus Control	BFRE versus Control	RT versus BFRE		Group × Time Interaction	Time	Group
Total cholesterol (TC), mmol/L										
T0	4.70 ± 0.87	4.54 ± 1.08	4.63 ± 0.97	−0.16	−0.08	−0.09	*F*	4.266	7.241	4.608
T3	4.86 ± 0.80	4.27 ± 0.77	4.25 ± 0.79	−0.75*	−0.77*	0.03	*p*	0.005	0.002	0.012
T6	4.81 ± 0.81	4.14 ± 0.67	4.09 ± 0.63	−0.90#	−0.99#	0.08	η^2P	0.082	0.071	0.088
T3 versus T0	0.16 (−0.18, 0.50)	−0.26 (−0.61, 0.09)	−0.38(−0.72, −0.50)*							
T6 versus T0	0.11 (−0.23, 0.45)	−0.40(−0.74, −0.05)*	−0.54(−0.87, −0.20)#							
Triglyceride (TG), mmol/L										
T0	2.60 ± 0.74	2.51 ± 0.82	2.46 ± 0.89	−0.12	−0.17	0.06	*F*	5.578	13.236	3.691
T3	2.63 ± 0.77	2.27 ± 0.81	2.08 ± 0.70	−0.46	−0.75*	0.25	*p*	0.001	< 0.001	0.029
T6	2.67 ± 0.65	2.14 ± 0.78	2.00 ± 0.67	−0.74*	−1.02#	0.19	η^2P	0.105	0.122	0.072
T3 versus T0	0.03 (−0.23, 0.29)	−0.24 (−0.51, 0.27)	−0.38(−0.63, −0.12)*							
T6 versus T0	0.07 (−0.16, 0.30)	−0.37(−0.61, −0.14)#	−0.46(−0.69, −0.24)#							
High density lipoprotein cholesterol (HDL-C), mmol/L										
T0	1.20 ± 0.29	1.12 ± 0.32	1.21 ± 0.38	−0.26	0.03	−0.26	*F*	10.219	64.361	6.777
T3	1.23 ± 0.31	1.35 ± 0.32	1.52 ± 0.33	0.38	0.91*	−0.52	*p*	< 0.001	< 0.001	0.002
T6	1.27 ± 0.31	1.58 ± 0.30	1.70 ± 0.33	1.02#	1.34#	−0.38	η^2P	0.177	0.404	0.125
T3 versus T0	0.04 (−0.10, 0.18)	0.23(0.09, 0.38)#	0.31(0.17, 0.45)#							
T6 versus T0	0.08(0.05, 0.20)	0.46(0.33, 0.59)#	0.50(0.37, 0.62)#							
Low density lipoprotein cholesterol (LDL-C), mmol/L										
T0	2.92 ± 0.63	2.85 ± 0.52	2.78 ± 0.61	−0.12	−0.23	0.12	*F*	4.834	21.146	3.544
T3	2.90 ± 0.86	2.49 ± 0.62	2.51 ± 0.59	−0.54	−0.53	−0.03	*p*	0.001	< 0.001	0.033
T6	2.90 ± 0.92	2.41 ± 0.51	2.35 ± 0.53	−0.65*	−0.74*	0.12	η^2P	0.092	0.182	0.069
T3 versus T0	−0.02 (−0.20,0.17)	−0.36(−0.55, −0.18)#	−0.27(−0.46, 0.09)*							
T6 versus T0	−0.02 (−0.23,0.21)	−0.45(−0.66, −0.23)#	−0.43(−0.64, −0.23)#							

BFRE, blood flow-restrictive resistance exercise group; RT, moderate-intensity resistance training group; η^2P, partial eta-squared; T0, baseline; T3, at third month; T6, at sixth month; *, significant difference at p<0.05; #, significant difference at p< 0.001.

group. At the sixth month of intervention, dyslipidemia in both exercise groups improved significantly compared with the control group (p< 0.05), with no significant difference in blood lipids between the two exercise groups (p > 0.05).

Table 6 shows the changes in body composition. The results of repeated measures ANOVA indicate that the main effect of time and the interaction effect of (group × time) on WHtR, BMI, FM, FMI, SMI, ASMI were significant (p< 0.001), indicating that the improvement effect of exercise intervention on these indicators became more pronounced over time. Compared with baseline, from the third month of intervention, WHtR, BMI, FM, FMI, SMI, ASMI showed significant improvements in both exercise groups (p< 0.05).

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TABLE 6 Effects of interventions on body composition among the three groups [mean ± SD or mean difference (95% CI)].

Indexs and time points	Group (n=98)			Cohen's d			Repeated measurement analysis of variance			
	Control (n=33)	RT (n=31)	BFRE (n=34)	RT versus Control	BFRE versus Control	RT versus BFRE		Group × Time Interaction	Time	Group
Waist-to-height ratio (WHtR), kg/m										
T0	0.56 ± 0.03	0.56 ± 0.04	0.55 ± 0.03	0.00	−0.33	0.29	*F*	143.912	240.453	8.817
T3	0.56 ± 0.03	0.54 ± 0.04	0.53 ± 0.03	−0.57*	−1.00#	0.29	*p*	<0.001	<0.001	<0.001
T6	0.57 ± 0.03	0.51 ± 0.03	0.51 ± 0.03	−1.67#	−1.67#	0.00	η^2P	0.752	0.717	0.157
T3 versus T0	0.003 (−0.001, 0.007)	−0.02(−0.03, −0.02)#	−0.03(−0.03, −0.02`)#							
T6 versus T0	0.01(0.01, 0.02)#	−0.05(−0.05, −0.04)#	−0.04(−0.04, −0.03)#							
Body mass index (BMI), kg/m^2										
T0	26.56 ± 1.58	26.02 ± 2.05	26.31 ± 1.88	−0.30	−0.14	−0.15	*F*	129.249	205.911	8.198
T3	27.00 ± 1.53	25.22 ± 1.98	25.73 ± 1.92	−1.01#	−0.73*	−0.26	*p*	< 0.001	< 0.001	< 0.001
T6	27.11 ± 1.61	24.14 ± 1.95	24.82 ± 1.88	−1.67#	−1.31#	−0.36	η^2P	0.731`	0.684	0.147
T3 versus T0	0.44(0.30, 0.59)#	−0.80(−0.96, −0.65)#	−0.58(−0.72, −0.43)#							
T6 versus T0	0.56(0.31, 0.80)#	−1.88(−2.13, −1.63)#	−1.48(−1.72, −1.24)#							
Fat mass (FM), kg										
T0	24.79 ± 3.42	22.97 ± 4.42	23.72 ± 4.60	−0.46	−0.26	−0.17	*F*	99.645	130.536	20.502
T3	26.15 ± 3.12	20.41 ± 4.07	21.87 ± 4.37	−1.59#	−1.12#	−0.35	*p*	<0.001	<0.001	<0.001
T6	26.80 ± 3.19	17.38 ± 3.59	19.25 ± 3.42	−2.78#	−2.28#	−0.53	η^2P	0.677	0.579	0.301
T3 versus T0	1.36(0.68, 2.04)#	−2.56(−3.26, −1.85)#	−1.87(−2.51, −1.22)#							
T6 versus T0	2.01(1.11, 2.90)#	−5.59(−6.51, −4.67)#	−4.47(−5.28, −3.66)#							
Lean mass (LM), kg										
T0	45.27 ± 8.57	44.84 ± 6.37	45.07 ± 6.70	−0.06	−0.03	−0.04	*F*	2.361	1.065	0.023
T3	45.06 ± 8.14	45.30 ± 6.59	45.44 ± 6.72	0.03	0.05	−0.02	*p*	0.062	0.341	0.977
T6	44.72 ± 8.44	45.56 ± 6.88	45.69 ± 7.14	0.11	0.12	−0.02	η^2P	0.047	0.011	0.000
T3 versus T0	−0.21 (−0.95,0.53)	0.46 (−0.30, 1.22)	0.37(−0.34, 1.07)							
T6 versus T0	−0.55 (−1.57,0.46)	0.72 (−0.33, 1.77)	0.62(−0.28, 1.52)							
Fat mass index (FMI), kg/m^2										
T0	9.49 ± 1.49	8.83 ± 1.48	9.08 ± 1.42	−0.44	−0.28	−0.17	*F*	106.561	143.034	24.246
T3	9.98 ± 1.19	7.86 ± 1.42	8.36 ± 1.32	−1.62#	−1.29#	−0.37	*p*	<0.001	<0.001	<0.001
T6	10.23 ± 1.31	6.68 ± 1.21	7.37 ± 1.06	−2.81#	−2.40#	−0.61	η^2P	0.692	0.601	0.338
T3 versus T0	0.49(0.24, 0.74)#	−0.98(−1.24, −0.72)#	−0.72(−0.95, −0.48)#							
T6 versus T0	0.75(0.43, 1.07)#	−2.15(−2.49, −1.82)#	−1.70(−2.00, −1.41)#							

(Continued)

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TABLE 6 Continued

Indexs and time points	Group (n=98)			Cohen's d			Repeated measurement analysis of variance			
	Control (n=33)	RT (n=31)	BFRE (n=34)	RT versus Control	BFRE versus Control	RT versus BFRE		Group × Time Interaction	Time	Group
Skeletal muscle mass index (SMI), kg/m^2										
T0	8.79 ± 0.80	8.91 ± 0.71	8.96 ± 0.71	0.16	0.23	−0.07	*F*	11.825	19.644	3.910
T3	8.71 ± 0.87	9.19 ± 0.58	9.23 ± 0.84	0.65*	0.61*	−0.06	*p*	<0.001	<0.001	0.023
T6	8.66 ± 0.93	9.41 ± 0.71	9.34 ± 0.85	0.90*	0.76*	0.09	η^2P	0.199	0.171	0.076
T3 versus T0	−0.08 (−0.25,0.09)	0.28(0.11, 0.45)#	0.27(0.12, 0.43)#							
T6 versus T0	−0.13 (−0.34,0.09)	0.50(0.28, 0.72)#	0.38(0.19, 0.57)#							
Appendicular skeletal muscle mass index (ASMI), kg/m^2										
T0	6.39 ± 0.60	6.47 ± 0.55	6.54 ± 0.54	0.14	0.26	−0.13	*F*	28.648	47.298	6.411
T3	6.30 ± 0.65	6.71 ± 0.53	6.82 ± 0.64	0.69*	0.81*	−0.19	*p*	<0.001	<0.001	0.002
T6	6.24 ± 0.70	6.99 ± 0.54	7.00 ± 0.65	1.20#	1.13#	−0.02	η^2P	0.376	0.332	0.119
T3 versus T0	−0.09 (−0.21,0.03)	0.24(0.17, 0.36)#	0.29(0.18, 0.39)#							
T6 versus T0	−0.15 (−0.31,0.01)	0.52(0.36, 0.67)#	0.46(0.33, 0.59)#							

BFRE, blood flow-restrictive resistance exercise group; RT, moderate-intensity resistance training group; η^2P, partial eta-squared; T0, baseline; T3, at third month; T6, at sixth month; *, significant difference at p< 0.05; #, significant difference at p< 0.001.

At the third month of intervention, increases in SMI [RT, 0.28 (0.11, 0.45); BFRE, 0.27 (0.12, 0.43)] and ASMI [RT, 0.24 (0.17, 0.36); BFRE, 0.29 (0.18, 0.39)] in both exercise groups was similar, while at the sixth month of intervention, the SMI and ASMI increase in the BFRE group [SMI, 0.38 (0.19, 0.57); ASMI, 0.46 (0.33, 0.59)] was lower than that of the RT group [SMI, 0.50 (0.28, 0.72), ASMI, 0.52 (0.36, 0.67)]. At the sixth month follow-up, WHtR, BMI, FM, FMI in the control group were significantly higher than baseline (p< 0.05). Compared with the control group, WHtR, BMI, FM, FMI, SMI, ASMI in two exercise groups were significantly improved since third month of intervention (p< 0.05). There were no significant differences in body composition between the two exercise groups (p > 0.05).

3.5 Secondary outcomes

Table 7 shows the muscle performance data. Compared with the baseline, the muscle performance of both exercise groups significantly increased from the third month of intervention (p< 0.05), with the grip strength of the RT group increasing by 1.7–2 times that of the BFRE group. At the sixth month of follow-up, the performance of the control group in the grip strength and five times-sit-to-stand tests significantly decreased than baseline (p< 0.05). Compared with the control group, the two exercise groups showed significantly better performance in five times-sit-to-stand test at the third month of intervention (p< 0.05). At the same time, the grip strength (d = 0.71, p = 0.021) and 6-m walking speed (d = 0.70, p = 0.005) of the RT group significantly increased compared with the control group, while the same improvement effect was observed in the BFRE group at the sixth month of intervention. There was no significant difference in muscle performance between the two exercise groups (p > 0.05).

3.6 Safety outcomes

Adverse events in this study were defined as any adverse symptoms or events related to the study measures or exercise intervention that occurred during the study. Serious adverse events were defined as those that were life-threatening, fatal, or resulted in permanent disability. During the research period, four events were defined as adverse events, with similar incidence rates in each group (RT, n = 2; BFRE, n = 1; control group, n = 1). One person in the RT group developed lateral epicondylitis of the humerus, which may be related to inappropriate force during resistance training and housework. After rest and treatment, her symptoms had been resolved. One participant in each of the RT and BFRE groups experienced similar symptoms of hypoglycemia at home, but their self-measured blood glucose levels were 4.1 mmol/L and 4.3 mmol/L, respectively, at the time. The symptoms resolved after eating, which was considered to be related to increased physical activity but not timely eating. One person in the control group experienced dizziness during a blood test taken while fasting, which may be due to excessive

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TABLE 7 Effects of interventions on muscle performance among three groups [mean ± SD or mean difference (95% CI)].

Indexs and time points	Group (n=98)			Cohen's d			Repeated measurement analysis of variance			
	Control (n=33)	RT (n=31)	BFRE (n=34)	RT versus Control	BFRE versus Control	RT versus BFRE		Group × Time Interaction	Time	Group
Grip strength test, kg										
T0	23.08 ± 5.18	22.94 ± 4.37	24.04 ± 5.20	−0.03	0.19	−0.23	*F*	240.830	601.558	3.149
T3	22.78 ± 4.88	26.06 ± 4.33	25.58 ± 5.00	0.71*	0.57	0.10	*p*	<0.001	<0.001	0.047
T6	22.70 ± 4.77	27.41 ± 4.37	26.68 ± 5.32	1.03#	0.79*	0.15	η^2P	0.835	0.864	0.062
T3 versus T0	−0.29(−0.57,−0.02)#	3.12(2.84, 3.40)#	1.54(1.27, 1.81)#							
T6 versus T0	−0.38(−0.69,−0.06)#	4.47(4.15, 4.80)#	2.64(2.34, 2.96)#							
Five times-sit-to-stand test, s										
T0	16.26 ± 3.09	15.72 ± 2.45	15.97 ± 2.47	−0.19	−0.10	−0.10	*F*	49.948	103.534	3.833
T3	16.48 ± 3.22	14.60 ± 2.14	14.84 ± 2.38	−0.68*	−0.58*	0.11	*p*	<0.001	<0.001	0.025
T6	16.61 ± 3.02	14.26 ± 2.23	14.13 ± 2.22	−0.88#	−0.94#	0.06	η^2P	0.513	0.521	0.075
T3 versus T0	0.22(−0.09, 0.54)	−1.11(−1.44, −0.79)#	−1.13(−1.44,−0.82)#							
T6 versus T0	0.35(0.05, 0.67)#	−1.45(−1.78, −1.14)#	−1.85(−2.15,−1.54)#							
6-m walking speed, s/m										
T0	1.08 ± 0.07	1.09 ± 0.07	1.07 ± 0.08	0.14	−0.13	0.27	*F*	40.884	99.069	5.087
T3	1.08 ± 0.08	1.13 ± 0.06	1.11 ± 0.05	0.70*	0.45	0.36	*p*	<0.001	<0.001	0.008
T6	1.07 ± 0.07	1.16 ± 0.07	1.15 ± 0.04	1.29#	1.41#	0.18	η^2P	0.463	0.510	0.097
T3 versus T0	−0.01(−0.02,0.01)	0.04(0.03, 0.06)#	0.05(0.03, 0.06)#							
T6 versus T0	−0.01 (−0.03, 0.003)	0.07(0.06, 0.09)#	0.08(0.07, 0.10)#							

BFRE, blood flow-restrictive resistance exercise group; RT, moderate-intensity resistance training group; η^2P, partial eta-squared; T0, baseline; T3, at third month; T6, at sixth month; *, significant difference at p< 0.05; #, significant difference at p< 0.001.

tension. In addition, the safety testing and two-week of adaptation training were completed before the exercise intervention. Those who could not continue due to illness or other reasons withdrew. No abnormal fluctuations in blood pressure or blood glucose occurred during exercise, and no serious adverse events, such as syncope, thrombosis, subcutaneous bleeding, falls, cardiovascular and cerebrovascular accidents occurred.

4 Discussion

The preliminary finding of this randomized controlled study was that for older adults with T2DM, BFRE was not only safe and easy to implement, but also achieved similar effects to moderate-intensity resistance training in improving patients' FPG, HbA1c, dyslipidemia, blood pressure, body composition, and muscle performance. Although there was not significant difference between the BFRE and RT in improving metabolic disorder and body composition in older adults with T2DM, from the trend of data changes, The BFRE had a faster effect in improving dyslipidemia, and the magnitude of increase in muscle mass and strength of the RT was greater.

Our results showed that moderate-intensity resistance exercise could significantly improve the FPG and HbA1c in older adults with T2DM. This was consistent with many previous research findings (26, 27). However, it is worth noting that the dropout rate of the RT group reached 34.04% in this study, and the main reason for withdrawal was feeling fatigued and sore in the early stages of exercise, which made them worried about worsening joint and muscle damage. In the cognition of older adults, resistance training is more suitable for those who are muscular, and participation in resistance training may increases the risk of having a heart attack, stroke or death in the elderly (6). Although the likelihood of these occurrences is small, it hinders their participation in resistance training (28).

Our research designed a BFRE program for older adults with T2DM. The main purpose of this design was to lower the load of resistance training, reduce the initial intensity and fatigue, and quickly obtain the protective effect of resistance training on blood glucose control. The results of this study show that six months of BFRE could effectively improve the FPG and HbA1c in older adults with T2DM. The effect was similar to that of moderate-intensity resistance exercise. Previous studies (14) have confirmed that BFRE can restrict blood flow by continuously pressurizing the limbs, causing severe fluctuations in the redox state of muscles due to ischemia and hypoxia, and increasing the high accumulation of reactive oxygen species (ROS). ROS activates 5'-AMP-activated protein kinase, enhancing GLUT4 mRNA and protein expression, increasing the abundance of GLUT4 in human skeletal muscle, and thus increasing glucose uptake. Therefore, most studies on BFRE use continuous pressure on the limbs during training to stimulate skeletal muscle hypertrophy and increase glucose uptake, but this can significantly increase exercise fatigue in subjects (13, 29, 30). Wang et al. (31) found that continuous compression during BFRE can improve muscle functional capacity more than intermittent compression, but higher fatigue phenomena also occur. In contrast, although intermittent BFRE can also bring fatigue, the recovery speed is faster. It is recommended that beginners adopt intermittent BFRE. Husmann et al. (32) pointed out that BFRE exacerbated the accumulation of exercise-induced, fatigue-related metabolites and prevented the recovery of contractile function during rest intervals. However, after two minutes of reperfusion, muscle contraction function recovered substantially, diminishing the impact of blood flow restriction on muscle fatigue. Therefore, in our BFRE program, there were 6.5 minutes of continuous compression on both the upper or lower limbs to stimulate skeletal muscle hypertrophy and increase skeletal muscle glucose uptake. Additionally, there were two minutes of blood flow reperfusion to reduce fatigue, allowing subjects to complete longer single-training sessions (30 minutes), fully exercise the muscles and joints of the body, and enhance exercise endurance.

In our study, although there was no significant difference in SBP between the two exercise groups and the control group, there was a significant decrease in both systolic and diastolic blood pressure compared to baseline. This shows that BFRE can steadily reduce the blood pressure of the older adults with T2DM. The impact of BFRE on blood pressure is still controversial. The experimental results of Rossow et al. (33) showed that only high-intensity resistance exercise showed a good antihypertensive effect on young men, while the effect of BFRE was not significant. The research results of Crisafulli et al. (34) and Maior et al. (35) indicate that young men only need to use relatively small amounts of muscles (such as grasping, biceps curling, or single-joint exercise) for low-load BFRE (≤ 40% 1-RM) to reduce post-exercise blood pressure. The meta-analysis results of Domingos et al. (36) suggested that although BFRE lead to greater post-exercise hypotension compared to traditional exercise, higher SBP and/or DBP were observed during BFRE, especially in hypertensive patients. Therefore, caution should be exercised when using BFRE. Another study suggests (37) that for older adults, the acute hemodynamic response caused by low-intensity BFRE is similar to that caused by high-load training, and can return to normal levels within 30 minutes after training with a more significant decrease in SBP. However, these studies were aimed at young adults and the non-diabetes population. The effect of BFRE on blood pressure in older adults with T2DM is rarely reported. Given previous studies suggesting that BFRE may cause fluctuations in blood pressure during exercise, in this study, we monitored the blood pressure of participants before exercise and found that abnormally elevated blood pressure may be related to factors such as climate change, poor sleep, and underlying disease changes. We tracked and treated patients with high blood pressure as necessary, so there were no significant fluctuations in blood pressure during exercise. After the six-month intervention, the blood pressure of participants in the BFRE group slowly declined with the extension of exercise time, but it did not cause a sudden drop in blood pressure, which has a protective effect on the cardiovascular health of the elderly.

In our research results, after exercise intervention, there was no significant change in lean mass, but WHtR, BMI, FM, and FMI were significantly reduced, and dyslipidemia was significantly improved in the RT and BFRE groups. This indicated that the two types of exercise could effectively reduce fat, especially abdominal fat, to achieve the goal of optimizing body shape and blood lipids. This is consistent with the research findings of Sun et al. (38). Abdominal obesity in elderly T2DM patients is often accompanied by more serious dyslipidemia (39, 40). The increased LDL-C has a lower affinity for vascular endothelial tissue and arterial wall proteoglycans, and is more prone to oxidation, leading to the formation of atherosclerotic plaques in the arteries (41). HDL-C dysfunction leads to the reduction of its anti-atherosclerosis, antioxidant, and anti-inflammatory properties, and accelerates the process of atherosclerosis (42). Elderly T2DM patients should be encouraged to exercise regularly in various ways to change abdominal obesity and dyslipidemia, in order to reduce the risk of cardiovascular complications. Compared to moderate-intensity resistance training, BFRE has a lower load during training, allowing athletes to use portable and lightweight exercise equipment to complete a variety of movements. This makes exercise more enjoyable and interesting without being limited by venue and time, making it more conducive to long-term persistence in elderly T2DM patients.

In this study, the SMI and ASMI of the two exercise groups were significantly improved compared to the baseline and control group, and the effects of the two exercise groups were similar. This may be because the hypoxic environment created by BFRE increases blood lactate concentration, accumulates metabolites, and promotes increased secretion of muscle hypertrophy hormones (such as growth hormone), synergistically promoting muscle protein synthesis (43). In addition, BFRE may further promote muscle hypertrophy by affecting the generation of nitric oxide or the activation of specific heat shock proteins (44). Therefore, even if low-intensity exercise were used, it could also achieve the muscle strengthening effect of moderate-intensity resistance training, which is of great significance to older adults with T2DM to prevent and treat sarcopenia. However, Lixandrão et al. (45) pointed out that muscle hypertrophy does not necessarily mean an increase in muscle strength. Even if both exercises can induce

similar muscle mass increases, high-intensity resistance training (> 65% 1-RM) significantly improves muscle strength growth compared to low-intensity BFRE. This may be because low-intensity BFRE has a relatively low promoting effect on neuromuscular driving ability. The ability to recruit muscle fibers cannot achieve the same effect as high-intensity training. In our study, although the increase in grip strength in the RT group was 1.7–2 times that of the BFRE group, there was no significant difference in grip strength, sit-to-stand and walking speed between the two exercise groups. This may be because our research mainly focused on older adults with T2DM. The strength and speed improvement of elderly people with sedentary habits was relatively limited, and diabetes patients tend to be weaker and more prone to fatigue. BFRE puts skeletal muscles in a hypoxic environment, leading to premature fatigue of type I muscle fibers. To resist external stress, more type II muscle fibers are activated to participate in work, and type II muscle fibers are the key to muscle hypertrophy and muscle strength growth. BFRE can improve the muscle mass and strength of older adults with T2DM with less effort, which is essential to preventing falls during exercise. After older adults improve their physical strength, balance, and stability through BFRE to a certain extent, their acceptance of exercise will be greatly enhanced, laying a good foundation for further acceptance of moderate-to-high-intensity resistance exercise or the other exercises.

5 Limitations of the study

This study also has some limitations, such as the intake of protein, carbohydrates, fat, and water in food affecting changes in lean mass and muscle mass. However, we did not provide a detailed evaluation of the participants' dietary behaviors or nutritional content of the food consumed, as recording was difficult for older adults. This makes it difficult to determine why six months of training did not significantly increase the lean mass of participants. A possible reason is that to control blood glucose, the participants mainly consumed light vegetables in their diet, with a reduced proportion of fruits, staple foods, meat, and fats. In addition, age-related muscle loss slowed down the growth of lean mass after exercise to a certain extent. In the future, the impact of combining dietary control with BFRE on T2DM will be explored further, in hopes of better promoting this exercise.

6 Conclusion

In this study, a BFRE program was designed combining intermittent restriction of limbs blood flow and low-intensity resistance training. The results showed that BFRE could effectively improve the metabolic disorder of blood glucose, dyslipidemia, and blood pressure in older adults with T2DM, and could also enhance the muscle function of patients by controlling abdominal obesity and reducing muscle loss. The effects of BFRE were similar to moderate-intensity resistance training. However, from the perspective of long-term data trends, BFRE may not be as effective as moderate-intensity resistance exercise in balancing muscle mass and strength in patients. Therefore, it is suggested that the older adults with T2DM should use BFRE for training under the guidance of professional medical staff at the beginning of exercise to obtain exercise adaptation in this relatively simple and easy way, then consider carrying out moderate- intensity resistance training, and choosing proper exercise methods according to their own conditions to better control diabetes.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding authors.

Ethics statement

This study protocol has been reviewed and approved for implementation by the Medical Ethics Committee of Shaoyang University and registered on the Chinese Clinical Trials Registry (Registration No.: ChiCTR2300074357). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

XM: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. YA: Writing – review & editing, Writing – original draft, Methodology. FL: Writing – review & editing, Writing – original draft, Investigation. XT: Writing – review & editing, Writing – original draft, Investigation. QL: Writing – review & editing, Writing – original draft, Investigation. YH: Writing – review & editing, Writing – original draft, Investigation. YZ: Writing – review & editing, Writing – original draft, Investigation. QM: Writing – review & editing, Writing – original draft, Investigation. LW: Writing – review & editing, Writing – original draft, Supervision, Methodology. FL: Writing – review & editing, Writing – original draft, Supervision, Methodology. QY: Writing – review & editing, Writing – original draft, Supervision, Methodology. FY: Writing – review & editing, Writing – original draft, Data curation. XY: Writing – review & editing, Writing – original draft, Software, Data curation. BH: Writing – review & editing, Writing – original draft, Supervision, Resources, Funding acquisition. LZ: Writing – review & editing, Writing – original draft, Software, Data curation. SR: Writing – review & editing, Writing – original draft, Supervision, Resources, Funding acquisition.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Li Y, Teng D, Shi X, Qin G, Qin Y, Quan H, et al. Prevalence of diabetes recorded in mainland China using 2018 diagnostic criteria from the American Diabetes Association: National cross sectional study. *BMJ*. (2020) 369:m997. doi: 10.1136/bmj.m997

2. China. Clinical guidelines for prevention and treatment of type 2 diabetes mellitus in the elderly in China (2022 edition). *Chin J Intern Med*. (2022) 30:2–51.

3. Izzo A, Massimino E, Riccardi G, Della Pepa G. A narrative review on sarcopenia in type 2 diabetes mellitus: prevalence and associated factors. *Nutrients*. (2021) 13:183. doi: 10.3390/nu13010183

4. Li Y, Lin S, Xu X, Jin W, Su Y, Yuan F, et al. Skeletal muscle HSF1 prevents insulin resistance by improving glucose utilization. *FASEB J*. (2022) 36:e22667. doi: 10.1096/fj.202201160RR

5. Kobayashi Y, Long J, Dan S, Johannsen NM, Talamoa R, Raghuram S, et al. Strength training is more effective than aerobic exercise for improving glycaemic control and body composition in people with normal-weight type 2 diabetes: a randomised controlled trial. *Diabetologia*. (2023) 66:1897–907. doi: 10.1007/s00125–023-05958–9

6. Burton E, Farrier K, Lewin G, Pettigrew S, Hill A-M, Airey P, et al. Motivators and barriers for older people participating in resistance training: A systematic review. *J Aging Phys Act*. (2017) 25:311–24. doi: 10.1123/japa.2015–0289

7. Lee J, Kim D, Kim C. Resistance training for glycemic control, muscular strength, and lean body mass in old Type 2 diabetic patients: A meta-analysis. *Diabetes Ther*. (2017) 8:459–73. doi: 10.1007/s13300–017-0258–3

8. Saatmann N, Zaharia O-P, Loenneke JP, Roden M, Pesta DH. Effects of blood flow restriction exercise and possible applications in type 2 diabetes. *Trends Endocrinol Metab*. (2021) 32:106–17. doi: 10.1016/j.tem.2020.11.010

9. Cook SB, Laroche DP, Villa MR, Barile H, Manini TM. Blood flow restricted resistance training in older adults at risk of mobility limitations. *Exp Gerontol*. (2017) 99:138–45. doi: 10.1016/j.exger.2017.10.004

10. Hughes L, Paton B, Rosenblatt B, Gissane C, Patterson SD. Blood flow restriction training in clinical musculoskeletal rehabilitation: a systematic review and meta-analysis. *Br J Sports Med*. (2017) 51:1003–11. doi: 10.1136/bjsports-2016–097071

11. Hwang PS, Willoughby DS. Mechanisms behind blood flow–restricted training and its effect toward muscle growth. *J Strength Cond Res*. (2019) 33:S167–79. doi: 10.1519/JSC.0000000000002384

12. Hughes L, Rosenblatt B, Haddad F, Gissane C, Mccarthy D, Clarke T, et al. Comparing the effectiveness of blood flow restriction and traditional heavy load resistance training in the post-surgery rehabilitation of anterior cruciate ligament reconstruction patients: A UK National Health Service randomised controlled trial. *Sports Med*. (2019) 49:1787–805. doi: 10.1007/s40279–019-01137–2

13. Wang J, Mogensen AG, Thybo F, Brandbyge M, Brorson J, Van Hall G, et al. Low-load blood flow-restricted resistance exercise produces fiber type-independent hypertrophy and improves muscle functional capacity in older individuals. *J Appl Physiol (1985)*. (2023) 134:1047–62. doi: 10.1152/japplphysiol.00789.2022

14. Christiansen D, Eibye KH, Hostrup M, Bangsbo J. Blood flow-restricted training enhances thigh glucose uptake during exercise and muscle antioxidant function in humans. *Metabolism*. (2019) 98:1–15. doi: 10.1016/j.metabol.2019.06.003

15. Miller EG, Nowson CA, Dunstan DW, Kerr DA, Menzies D, Daly RM. Effects of whey protein plus vitamin D supplementation combined with progressive resistance training on glycaemic control, body composition, muscle function and cardiometabolic risk factors in middle-aged and older overweight/obese adults with type 2 diabetes: A 24-week randomized controlled trial. *Diabetes Obes Metab*. (2021) 23:938–49. doi: 10.1111/dom.14299

16. Nascimento DDC, Rolnick N, Neto IVS, Severin R, Beal FLR. A useful blood flow restriction training risk stratification for exercise and rehabilitation. *Front Physiol*. (2022) 13:808622. doi: 10.3389/fphys.2022.808622

17. Federation. Definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia. Report of a WHO/IDF consultation (2016). Available online at: https://www.who.int/diabetes/publications/diagnosis_diabetes2006/en/.

18. Colberg SR, Sigal RJ, Fernhall B, Regensteiner JG, Blissmer BJ, Rubin RR, et al. Exercise and type 2 diabetes: The American College of Sports Medicine and the American Diabetes Association: Joint position statement. *Diabetes Care*. (2010) 33:e147–67. doi: 10.2337/dc10–9990

19. Colberg SR, Sigal RJ, Yardley JE, Riddell MC, Dunstan DW, Dempsey PC, et al. Physical activity/exercise and diabetes: A position statement of the American Diabetes Association. *Diabetes Care*. (2016) 39:2065–79. doi: 10.2337/dc16–1728

20. Elsayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, et al. 13. Older adults: standards of care in diabetes—2023. *Diabetes Care*. (2023) 46:S216–29. doi: 10.2337/dc23-S013

21. Hansen D, Niebauer J, Cornelissen V, Barna O, Neunhäuserer D, Stettler C, et al. Exercise prescription in patients with different combinations of cardiovascular disease risk factors: a consensus Statement from the EXPERT Working Group. *Sports Med*. (2018) 48:1781–97. doi: 10.1007/s40279-018-0930-4

22. Dai X, Zhai L, Chen Q, Miller JD, Lu L, Hsue C, et al. Two-year-supervised resistance training prevented diabetes incidence in people with prediabetes: A randomised control trial. *Diabetes Metab Res Rev*. (2019) 35:e3143. doi: 10.1002/dmrr.3143

23. Garber CE, Blissmer B, Deschenes MR, Franklin BA, Lamonte MJ, Lee IM, et al. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults. *Med Sci Sports Exerc*. (2011) 43:1334–59. doi: 10.1249/MSS.0b013e318213fefb

24. Zhuang M, Shi J, Liu J, He X, Chen N. Comparing the efficacy of low-load resistance exercise combined with blood flow restriction versus conventional-load resistance exercise in Chinese community-dwelling older people with sarcopenic obesity: a study protocol for a randomised controlled trial. *BMC Geriatr*. (2023) 23:874. doi: 10.1186/s12877–023-04592–9

25. Sieljacks P, Degn R, Hollaender K, Wernbom M, Vissing K. Non-failure blood flow restricted exercise induces similar muscle adaptations and less discomfort than failure protocols. *Scand J Med Sci Sports*. (2019) 29(3):336–47. doi: 10.1111/sms.13346

26. Ciumărnean L, Milaciu MV, Negrean V, Orășan OH, Vesa SC, Sălăgean O, et al. Cardiovascular risk factors and physical activity for the prevention of cardiovascular diseases in the elderly. *Int J Environ Res Public Health*. (2021) 19:207. doi: 10.3390/ijerph19010207

27. Jansson AK, Chan LX, Lubans DR, Duncan MJ, Plotnikoff RC. Effect of resistance training on HbA1c in adults with type 2 diabetes mellitus and the moderating effect of changes in muscular strength: a systematic review and meta-analysis. *BMJ Open Diabetes Res Care*. (2022) 10:e002595. doi: 10.1136/bmjdrc-2021–002595

28. Fragala MS, Cadore EL, Dorgo S, Izquierdo M, Kraemer WJ, Peterson MD, et al. Resistance training for older adults: position statement from the National Strength and Conditioning Association. *J Strength Cond Res*. (2019) 33:2019–52. doi: 10.1519/JSC.0000000000003230

29. Karabulut M, Cramer JT, Abe T, Sato Y, Bemben MG. Neuromuscular fatigue following low-intensity dynamic exercise with externally applied vascular restriction. *J Electromyogr Kinesiol*. (2010) 20:440–7. doi: 10.1016/j.jelekin.2009.06.005

30. Chen N, He X, Zhao G, Lu L, Ainsworth BE, Liu Y, et al. Efficacy of low-load resistance training combined with blood flow restriction vs. high-load resistance training on sarcopenia among community-dwelling older Chinese people: study protocol for a 3-arm randomized controlled trial. *Trials*. (2021) 22:518. doi: 10.1186/s13063-021-05495-z

31. Wang Y, Li Z, Tongtong C, Zhang W, Li X. Effect of continuous and intermittent blood flow restriction deep-squat training on thigh muscle activation and fatigue levels in male handball players. *Sci Rep*. (2023) 13:19152. doi: 10.1038/s41598–023-44523–7

32. Husmann F, Mittlmeier T, Bruhn S, Zschorlich V, Behrens M. Impact of blood flow restriction exercise on muscle fatigue development and recovery. *Med Sci Sports Exerc*. (2018) 50:436–46. doi: 10.1249/MSS.0000000000001475

33. Rossow LM, Fahs CA, Sherk VD, Seo D-I, Bemben DA, Bemben MG. The effect of acute blood-flow-restricted resistance exercise on postexercise blood pressure. *Clin Physiol Funct Imaging*. (2011) 31:429–34. doi: 10.1111/cpf.2011.31.issue-6

34. Crisafulli A, De Farias RR, Farinatti P, Lopes KG, Milia R, Sainas G, et al. Blood flow restriction training reduces blood pressure during exercise without affecting Metaboreflex activity. *Front Physiol*. (2018) 9:1736. doi: 10.3389/fphys.2018.01736

35. Maior AS, Simão R, Martins MSR, de Salles BF, Willardson JM. Influence of blood flow restriction during low-intensity resistance exercise on the postexercise hypotensive response. *J Strength Cond Res*. (2015) 29:2894–9. doi: 10.1519/JSC.0000000000000930

36. Domingos E, Polito MD. Blood pressure response between resistance exercise with and without blood flow restriction: A systematic review and meta-analysis. *Life Sci*. (2018) 209:122–31. doi: 10.1016/j.lfs.2018.08.006

37. Centner C, Wiegel P, Gollhofer A, König D. Effects of blood flow restriction training on muscular strength and hypertrophy in older individuals: A systematic review and meta-analysis. *Sports Med*. (2018) 49:95–108. doi: 10.1007/s40279-018-0994-1

38. Sun L. Effects of blood flow restriction training on anthropometric and blood lipids in overweight/obese adults: meta-analysis. *Front Physiol*. (2022) 13:1039591. doi: 10.3389/fphys.2022.1039591

39. Lee JS, Chang P-Y, Zhang Y, Kizer JR, Best LG, Howard BV. Triglyceride and HDL-C dyslipidemia and risks of coronary heart disease and ischemic stroke by glycemic dysregulation status: The strong heart study. *Diabetes Care*. (2017) 40:529–37. doi: 10.2337/dc16–1958

40. Bhatt DL, Steg PG, Miller M, Brinton EA, Jacobson TA, Ketchum SB, et al. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. *N Engl J Med*. (2019) 380:11–22. doi: 10.1056/NEJMoa1812792

41. Banach M, Surma S, Reiner Z, Katsiki N, Penson PE, Fras Z, et al. Personalized management of dyslipidemias in patients with diabetes-it is time for a new approach, (2022). *Cardiovasc Diabetol*. (2022) 21:263. doi: 10.1186/s12933–022-01684–5

42. Kaze AD, Santhanam P, Musani SK, Ahima R, Echouffo-Tcheugui JB. Metabolic dyslipidemia and cardiovascular outcomes in type 2 diabetes mellitus: findings from the look AHEAD study. *J Am Heart Assoc*. (2021) 10:e016947. doi: 10.1161/JAHA.120.016947

43. Franz A, Ji S, Bittersohl B, Zilkens C, Behringer M. Impact of a six-week prehabilitation with blood-flow restriction training on pre- and postoperative skeletal muscle mass and strength in patients receiving primary total knee arthroplasty. *Front Physiol*. (2022) 13:881484. doi: 10.3389/fphys.2022.881484

44. Nielsen JL, Aagaard P, Prokhorova TA, Nygaard T, Bech RD, Suetta C, et al. Blood flow restricted training leads to myocellular macrophage infiltration and upregulation of heat shock proteins, but no apparent muscle damage. *J Physiol*. (2017) 595:4857–73. doi: 10.1113/JP273907

45. Lixandrão ME, Ugrinowitsch C, Berton R, Vechin FC, Conceição MS, Damas F, et al. Magnitude of muscle strength and mass adaptations between high-load resistance training versus low-load resistance training associated with blood-flow restriction: A systematic review and meta-analysis. *Sports Med*. (2017) 48:361–78.

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A mendelian randomisation study of the causal effect of exercise intensity on the development of type 2 diabetes

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Objective: This study examines the causal effects of varying exercise intensities on type 2 diabetes mellitus (T2D) through Mendelian randomization (MR) analysis, using genetic variants as instrumental variables.

Methods: A two-sample MR analysis was performed, employing Inverse Variance Weighted (IVW) as the primary method, supported by weighted median, MR-Egger regression, MR-PRESSO, and MR robustness-adjusted contour scores. Data were obtained from the International Exercise Genetics Database (IEGD) and the Global Diabetes Research Consortium (GRC), encompassing over 150,000 individuals for exercise intensity and around 200,000 T2D patients and controls. SNPs linked to exercise intensity were selected based on genome-wide significance ($P < 5 \times 10^{-8}$) and linkage disequilibrium criteria (distance >10,000 kb, $r^2 < 0.001$).

Results: The IVW analysis suggested that high-intensity exercise might reduce T2D risk, but the association was not statistically significant (OR = 0.667, 95% CI = 0.104–4.255, $P = 0.667$). The wide confidence interval indicates uncertainty in the effect estimate. Low-intensity exercise showed no significant effect on T2D risk (OR ~ 1.0). Sensitivity analyses, including weighted median and MR-Egger regression, confirmed no significant association between high-intensity exercise and T2D risk. The MR-PRESSO analysis found no significant outliers, and the global test for pleiotropy was non-significant ($P = 0.455$). Cochran's Q test for heterogeneity in the IVW analysis was non-significant (Q = 12.45, $P = 0.234$), indicating consistency among SNP-derived estimates.

Conclusion: High-intensity exercise potentially reduces T2D risk, but the association is not statistically significant. Further research is needed to understand the complex relationship between exercise intensity and T2D.

KEYWORDS

exercise intensity, type 2 diabetes, Mendelian randomization, causal inference, inverse variance weighted

1 Introduction

Type 2 diabetes (T2D), one of the most prevalent chronic diseases globally, presents a significant public health challenge due to its rising prevalence and associated severe complications (Sousa et al., 2024; Wang et al., 2024). Given its substantial impact on individual health and socioeconomics, strategies for the prevention and management of

T2D have garnered extensive attention from researchers and public health policymakers worldwide (Legasto-Mulvale et al., 2023). Exercise is well-recognized as a crucial measure for preventing and managing T2D (Freeby and Lane, 2023). However, the precise relationship between exercise intensity and T2D risk remains unclear (Poulsen and Moore, 2023; Nyström et al., 2022). Early observational studies suggested that moderate to high-intensity exercise is linked to a reduced risk of T2D, but these studies faced challenges in establishing a causal relationship due to design limitations.

Mendelian randomization (MR), a method that uses genetic variation as an instrumental variable to infer causal relationships between exposures and outcomes, has gained prominence in recent years (İlaslan and Adıbelli, 2023). MR can address issues of confounding factors and reverse causation inherent in traditional observational studies, The association between exposure factors and outcome factors can be articulated at the genetic level, and this association is causal with reliable results. At the same time, it is an excellent experimental method that avoids the ethical problems associated with animal and clinical experiments. (Zhu et al., 2023). This study aimed to investigate the potential causal effects of exercise intensity on T2D risk using MR (Kwon et al., 2023; Heikkilä et al., 2023). By analyzing extensive genetic data, we sought to understand how exercise intensity influences T2D risk through genetic pathways (Shabab et al., 2023). Additionally, we focused on specific genetic variants that might play key roles in the relationship between exercise and T2D.

First, we review the epidemiological background of T2D and the role of exercise in its prevention (Hu et al., 2024). Second, we introduce the rationale for MR methods and their application in exploring the exercise-T2D relationship (Cai et al., 2022a). Next, we detail the study design, including data sources, analytical methods, and potential limitations. Finally, we discuss the significance of our findings and their implications for future research directions.

2 Experimental methodology

2.1 Sources of information

The data for this study were obtained from two primary databases: the International Exercise Genetics Database (IEGD) and the Global Diabetes Research Consortium (GRC). The IEGD includes data on over 150,000 individuals, covering exercise habits, intensity, and related genetic markers. The GRC provides detailed medical records and genetic information for approximately 200,000 patients and controls related to T2D incidence.

2.2 Data organization

For Mendelian randomization (MR) analyses, we ensured the genetic variants (SNPs) used were strongly associated with exercise intensity and not confounded by other factors. We selected SNPs with a strong association ($P < 5 \times 10^{-8}$) and used the European Population Thousand Genomes Database to calculate linkage disequilibrium (LD) for screening independent SNPs with genetic distances >10,000 kb and $r^2 < 0.001$. SNPs with minor allele frequencies <0.01 and F-values <10 were excluded to minimize weak instrument bias (Qian et al., 2024).

2.3 Statistical processing

2.3.1 Two-sample MR analysis

We used Inverse Variance Weighted (IVW) as the primary method to assess the causal effect of exercise intensity on T2D risk. To validate the results' robustness, we applied additional MR methods, including Weighted Median, MR-Egger regression, MR-Robust Adjusted Profile Score (MR-RAPS), and MR-Pleiotropy Residual Sum and Outlier (MR-PRESSO).

2.3.2 Sensitivity analysis

We used Cochran's Q statistic for IVW to test instrument heterogeneity. MR-Egger regression intercept assessed horizontal pleiotropy. The MR-PRESSO global test further evaluated heterogeneity in MR causal estimation.

2.3.3 Inverse MR analysis

To examine the potential causal effect of T2D on exercise intensity, we applied the described MR methods, using T2D as the exposure and exercise intensity as the outcome.

All statistical analyses were conducted using R software (version 4.1.1). The causal effect of exercise intensity on T2D risk was expressed as Odds Ratio (OR) with 95% Confidence Interval (CI). The effect of T2D on exercise intensity was expressed as effect size (β) with 95% CI. Given multiple comparisons, a Bonferroni-corrected p-value <0.0056 (0.05/9, two-sided) was deemed statistically significant.

3 Experimental results

3.1 Screening and validation of instrumental variables

We began with a rigorous screening of potential instrumental variables. Utilizing extensive genomic data, we identified multiple genetic markers associated with exercise intensity. By integrating genetic correlations and biomarkers affecting exercise performance, we selected 15 single nucleotide polymorphisms (SNPs) closely related to exercise intensity as instrumental variables. These SNPs, distributed across different genetic loci, are associated with the regulation of exercise capacity and muscle function.

To verify the validity of these SNPs as instrumental variables, we calculated the joint F-statistic for each, with all results exceeding 10, indicating strong explanatory power and minimal weak instrument bias.

3.2 Association analysis between exercise intensity and type 2 diabetes risk

Using Mendelian randomization, we analyzed the association between exercise intensity and T2D risk. The Inverse Variance Weighted method showed that high-intensity exercise was

TABLE 1 Mendelian randomization for Strenuous sports or other exercises and Type 2 Diabetes Mellitus.

		Type 2 diabetes mellitus		
		OR estimate (95% CI)	*P*-value	Beta
Strenuous sports or other exercises	MR Egger	4.900 (0.001–20.634)	0.777	1.589
	Inverse variance weighted	0.667 (0.104–4.255)	0.667	−0.406
	Weighted mode	2.001 (0.633–6.369)	0.237	0.697

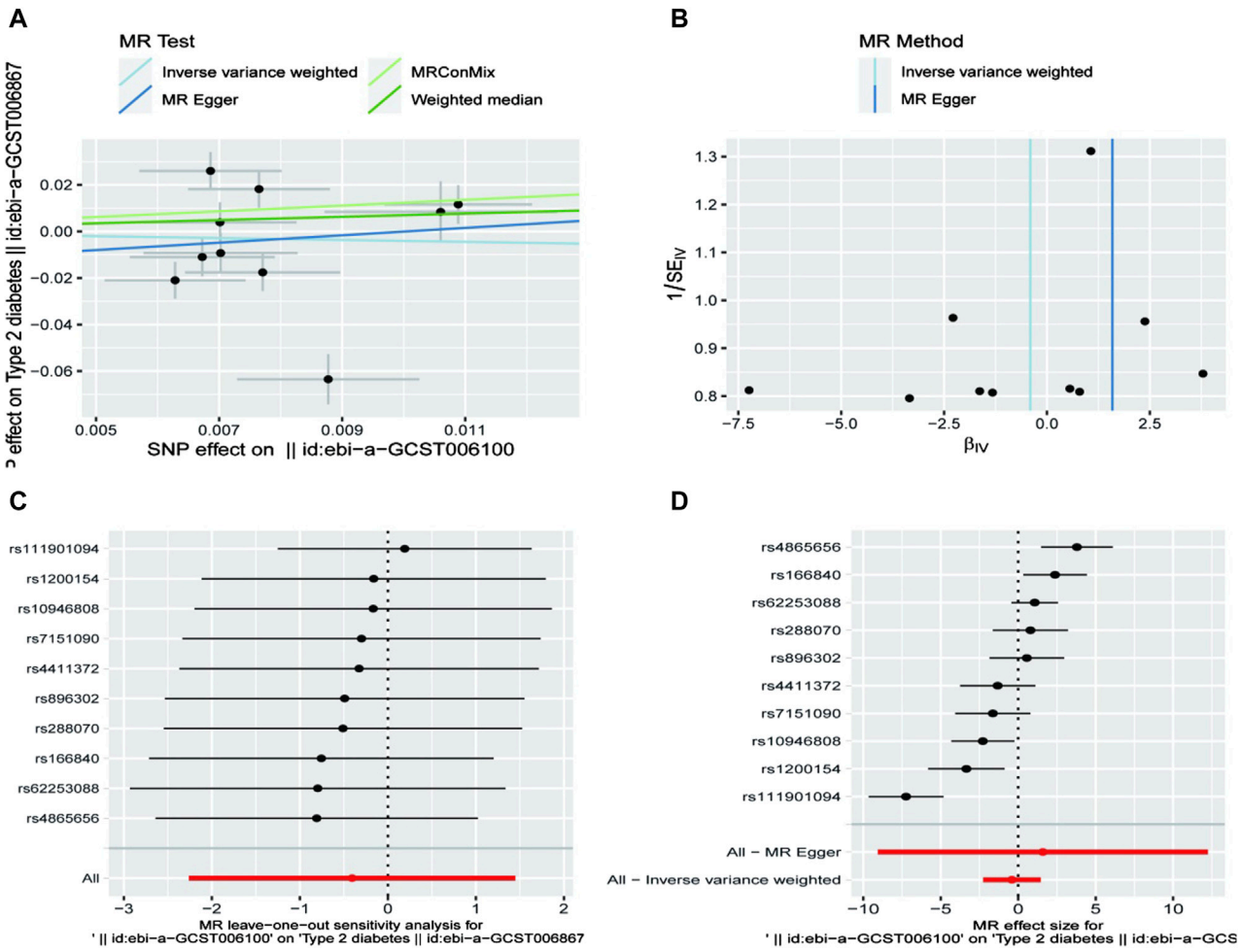

FIGURE 1
Mendelian Randomisation Analysis of SNP Effects on Type 2 Diabetes.

associated with a reduced risk of T2D, although the result was not statistically significant (OR = 0.667, 95% CI = 0.104–4.255, *P* = 0.667). Low-intensity exercise showed no significant effect on T2D risk. The MR-Egger method similarly found no significant association between vigorous exercise and T2D (OR = 4.900, 95% CI = 0.001–20.634, *P* = 0.777). The weighted mode approach also showed no significant effect (OR = 2.001, 95% CI = 0.633–6.369, *P* = 0.237) (Table 1/Figure 1).

Sensitivity analyses, including MR-Egger regression and Leave-one-out cross-validation, supported the robustness of these findings. MR-Egger regression revealed no significant pleiotropy bias ($P > 0.05$), enhancing the credibility of our results (Table 2).

4 Discussion

This study explores the complex relationship between exercise intensity and the risk of developing type 2 diabetes (T2D). Our findings provide important insights into how exercise impacts T2D risk (Wagner et al., 2023; Cai et al., 2022b).

TABLE 2 Sensitivity and Heterogeneity Analysis of Maternal Strenuous sports or other exercises and Type 2 Diabetes Mellitus.

	Heterogeneity test						Pleiotropy test		
	MR-Egger			Inverse variance weighted			MR-Egger		
	Q	Q_df	Q_pval	Q	Q_df	Q_pval	intercept	se	p
Strenuous sports or other exercises	64.94	8	0.178	66.07	9	0.207	0.02	0.04	0.718

The association between high-intensity exercise and reduced T2D risk, while not statistically significant (Zimmer et al., 2023), suggests a potential trend. This indicates that high-intensity exercise, although beneficial, may not have as substantial an impact on T2D prevention as previously assumed (Faria et al., 2024; Kartinah et al., 2024; Rouault et al., 2023; Tayebi et al., 2024). This could be due to the multifaceted biological pathways through which high-intensity exercise exerts its effects (Yu et al., 2024; Jain et al., 2023). Therefore, it is important not to consider high-intensity exercise as a definitive solution for T2D prevention.

Our study found no significant effect of low-intensity exercise on T2D risk. This challenges the conventional belief that any form of exercise positively affects diabetes prevention (Zeng et al., 2024). It implies that merely increasing exercise volume without considering intensity, diet, lifestyle, and genetic factors might not significantly reduce T2D risk (Zhang et al., 2023; Yang et al., 2023; Zhang Bo et al., 2024; Clayton-Chubb et al., 2023). Thus, a comprehensive approach incorporating dietary management, lifestyle modifications, and genetic background consideration is essential for T2D prevention and management.

Our study highlights the need for future research. Although we used Mendelian randomization to infer causality, our findings require validation in broader populations and varied contexts (Belko et al., 2023; Cai et al., 2020; Cai et al., 2021; Athari et al., 2024). Further exploration is needed to understand how exercise intensity influences T2D risk through metabolic pathways, insulin sensitivity, and pancreatic β-cell function (Patel et al., 2023; Zhang Jinghua et al., 2024; Muñoz et al., 2024; Romeres et al., 2024). These factors could significantly impact the relationship between exercise intensity and T2D risk.

It is also crucial to consider individual differences in responses to exercise intensity (Khan et al., 2023; Menek and Kaya, 2024). Genetic, lifestyle, and environmental factors may cause varying responses among individuals to the same exercise intensity (Sun et al., 2024; Cai and Wang, 2024). Future studies should account for these individual differences to better understand how exercise affects T2D risk.

5 Strengths and limitations

Although this study explores the potential causal effects of different exercise intensities on type 2 diabetes mellitus (T2D) risk using Mendelian randomization (MR) methods, there are still some limitations to note.

5.1 Strengths

5.1.1 Utilization of Mendelian Randomization (MR) method

The MR method leverages genetic variations as instrumental variables, effectively controlling for confounding factors and reverse causation present in traditional observational studies, thereby providing more reliable causal inferences.

5.1.2 Diverse statistical techniques

This study employs multiple robust statistical techniques, including Inverse Variance Weighted (IVW), weighted median, MR-Egger regression, and MR-PRESSO. These methods help to reduce bias from horizontal pleiotropy and other confounding factors, enhancing the reliability of the results.

5.2 Limitations

5.2.1 Sample size and statistical power

Although we used data from two large databases, the association between high-intensity exercise and T2D risk did not reach statistical significance. This may be due to an insufficient sample size, leading to a lack of statistical power to detect subtle but true causal effects.

5.2.2 Limitations of genetic instruments

The single nucleotide polymorphisms (SNPs) selected as instrumental variables in this study are limited to known genetic markers associated with exercise intensity, which may omit some important genetic variants. Additionally, the selected SNPs may have unknown horizontal pleiotropy, although we attempted to minimize this impact through various methods.

5.3 Future improvements

5.3.1 Increasing sample size

Future studies should increase the sample size, especially including more diverse populations from different races and regions, to improve statistical power and the generalizability of the results.

5.3.2 Integration of multi-omics data

Besides genetic data, integrating epigenomics, transcriptomics, metabolomics, and other multi-omics data will provide a comprehensive analysis of the complex relationship between exercise intensity and T2D risk.

6 Conclusion

In summary, increased exercise intensity may reduce the risk of T2D by modulating amino acid metabolism, particularly branched-chain and aromatic amino acids. This finding provides a new perspective on the prevention and treatment of T2D and emphasizes the importance of exercise in the health management of T2D. Future studies should further explore the complex interactions between exercise and T2D pathogenesis in order to develop more precise and effective prevention and treatment strategies.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

FY: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Software, Validation, Writing–original draft, Writing–review and editing. HB: Investigation, Writing–review and editing. HQ: Data curation, Formal Analysis, Methodology, , Writing–review and editing. SL: Project administration, Supervision, Validation, Writing–review and editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

Athari, S. Z., Bavil, F. M., Keyhanmanesh, R., Lotfi, H., Sajed, Y., Delkhosh, A., et al. (2024). Voluntary exercise improves pulmonary inflammation through NF-κB and Nrf2 in type 2 diabetic male rats. *Iran. J. Basic Med. Sci.* 27 (1), 74–80. doi:10.22038/IJBMS.2023.70416.15307

Belko, S., Hutchinson, M., Hayden, G., and Pugliese, R. (2023). Co-Designing diabetes care with patients. *J. diabetes Sci. Technol.* 18 (1), 53–58. doi:10.1177/19322968231213394

Cai, X., Gao, J., Liu, S., Wang, M., Hu, J., Hong, J., et al. (2022b). Hepatic steatosis index and the risk of type 2 diabetes mellitus in China: insights from a general population-based cohort study. *Dis. MARKERS* 2022, 3150380. doi:10.1155/2022/3150380

Cai, X., Wang, M., Liu, S., Yuan, Y., Hu, J., Zhu, Q., et al. (2022a). Establishment and validation of a nomogram that predicts the risk of type 2 diabetes in obese patients with non-alcoholic fatty liver disease: a longitudinal observational study. *Am. J. Transl. Res.* 14 (7), 4505–4514. PMID: 35958467. doi:10.1155/2022/3150380

Cai, X., Zhu, Q., Cao, Y., Liu, S., Wang, M., Wu, T., et al. (2021). A prediction model based on noninvasive indicators to predict the 8-year incidence of type 2 diabetes in patients with nonalcoholic fatty liver disease: a population-based retrospective cohort study. *Biomed. Res. Int.* 2021, 5527460. doi:10.1155/2021/5527460

Cai, X., Zhu, Q., Wu, T., Zhu, B., Aierken, X., Ahmat, A., et al. (2020). Development and validation of a novel model for predicting the 5-year risk of type 2 diabetes in patients with hypertension: a retrospective cohort study. *Biomed. Res. Int.* 2020, 9108216. doi:10.1155/2020/9108216

Cai, Z., and Wang, L. (2024). Letter to the Editor on "Effectiveness of combined aerobic and resistance exercise on cognition, metabolic health, physical function, and health-related quality of life in middle-aged and older adults with type 2 diabetes mellitus: a systematic review and meta-analysis. *ARCHIVES Phys. Med. REHABILITATION* 105, 798–799. doi:10.1016/j.apmr.2023.11.015

Clayton-Chubb, D., Kemp, W. W., Majeed, A., Lubel, J. S., Woods, R. L., Tran, C., et al. (2023). Metabolic dysfunction-associated steatotic liver disease in older adults is associated with frailty and social disadvantage. *LIVER Int.* 44 (1), 39–51. doi:10.1111/liv.15725

Faria, de, Rogatto, R., Siqueira, de, Freitas, S., Haddad, F. A., and Martinelli Filho, M. (2024). The Six Pillars of lifestyle medicine in managing noncommunicable diseases - the gaps in cguidelines. *Arq. Bras. Cardiol.* 120 (12), e20230408. doi:10.36660/abc.20230408

Freeby, M., and Lane, K. (2023). Treating obesity in type 1 diabetes mellitus - review of efficacy and safety. *Curr. Opin. Endocrinol. Diabetes Obes.* 31 (1), 1–7. doi:10.1097/MED.0000000000000841

Heikkilä, A., Eeva, P., Tytti, M.-L., Korpelainen, R., Huttunen, J., Rahkonen, M., et al. (2023). Level, types and determinants of physical activity in children with type 1 diabetes and their parents: a cross-sectional study. *Diabet. Med.* 41 (1), e15149. doi:10.1111/dme.15149

Hu, S., Chen, Xi, Zheng, Gu, Zhao, Y., Liu, X., Li, Y., et al. (2024). The prevalence and risk factors of blepharoptosis in an elderly asian population. *AESTHETIC Plast. Surg.* 48, 1298–1305. doi:10.1007/s00266-023-03804-2

İlaslan, E., and Adıbelli, D. (2023). Exploring disease management experiences of individuals with type 2 diabetes during the COVID-19 pandemic: a qualitative study. *Clin. Nurs. Res.* 33 (1), 51–59. doi:10.1177/10547738231201996

Jain, R., Begum, N., Rajan, S., Tryphena, K. P., and Khatri, D. K. (2023). Role of F-actin-mediated endocytosis and exercise in mitochondrial transplantation in an experimental Parkinson's disease mouse model. *MITOCHONDRION* 74, 101824. doi:10.1016/j.mito.2023.11.007

Kartinah, N., Rusli, H., Ilyas, E., Andraini, T., Paramita, N., Santoso, D., et al. (2024). High-intensity interval training increases AMPK and GLUT4 expressions via FGF21 in skeletal muscles of diabetic rats. *J. Adv. Biotechnol. Exp. Ther.* 7 (1), 136. doi:10.5455/jabet.2024.d12

Khan, A. R., Alnoud, M. A. H., Ali, H., Ali, I., Ahmad, S., Ul Hassan, S. S., et al. (2023). Beyond the beat: a pioneering investigation into exercise modalities for alleviating diabetic cardiomyopathy and enhancing cardiac health. *Curr. PROBLEMS Cardiol.* 49 (2), 102222. doi:10.1016/j.cpcardiol.2023.102222

Kwon, S., Lee, S.-R., Choi, E.-K., Jung, J. H., Han, K. D., Oh, S., et al. (2023). Impact of unhealthy lifestyles on patients with atrial fibrillation at low risk of stroke: a nationwide cohort study. *Am. J. Med.* 137 (1), 37–46.e6. doi:10.1016/j.amjmed.2023.09.012

Legasto-Mulvale, J. M., Inness, E. L., Thompson, A. N., Chandran, N., Mathur, S., and Salbach, N. M. (2023). Adverse events during submaximal aerobic exercise testing in people with subacute stroke: a scoping review. *J. Neurologic Phys. Ther.* 48 (1), 27–37. doi:10.1097/NPT.0000000000000445

Menek, M. Y., and Kaya, A. K. (2024). Comparison of home exercise under supervision and self home exercise in pregnant women with gestational diabetes: randomized controlled trial. *ARCHIVES Gynecol. OBSTETRICS* 309, 1075–1082. doi:10.1007/s00404-023-07339-4

Muñoz, V. R., Vieira, R. F. L., Katashima, C. K., Gaspar, R. C., Lino, M., Trombeta, J. C. D. S., et al. (2024). Rho-kinase is differentially expressed in the adipose tissue of rodent and human in response to aging, sex, and acute exercise. *JOURNALS GERONTOLOGY Ser. A-BIOLOGICAL Sci. Med. Sci.* 79, glae001. doi:10.1093/gerona/glae001

Nyström, T., Schwarz, E., Dahlqvist, S., Wijkman, M., Ekelund, M., Holmer, H., et al. (2022). Evaluation of effects of continuous glucose monitoring on physical activity habits and blood lipid levels in persons with type 1 diabetes managed with multiple daily insulin injections: an analysis based on the GOLD randomized trial (GOLD 8). *J. diabetes Sci. Technol.* 18 (1), 89–98. doi:10.1177/19322968221101916

Patel, V., Aggarwal, K., Dhawan, A., Singh, B., Shah, P., Sawhney, A., et al. (2023). Protein supplementation: the double-edged sword. *Proc. Bayl. Univ. Med. Cent.* 37 (1), 118–126. doi:10.1080/08998280.2023.2280417

Poulsen, S. L., and Moore, S. J. (2023). Exercise affects fatty acid oxidation and lipid droplets in patients with type 2 diabetes. *J. PHYSIOLOGY-LONDON* 602 (1), 11–12. doi:10.1113/JP285041

Qian, H., Zuo, Y., Wen, S., Wang, X., Liu, Y., and Li, T. (2024). Impact of exercise training on gut microbiome imbalance in obese individuals: a study based on Mendelian randomization analysis. *Front. Physiology* 14, 1264931. doi:10.3389/fphys.2023.1264931

Romeres, D., Yadav, Y., Ruchi, F. N. U., Carter, R., Cobelli, C., Basu, R., et al. (2024). Hyperglycemia suppresses lactate clearance during exercise in type 1 diabetes. *J. Clin. Endocrinol. & METABOLISM* 109, e1720–e1731. doi:10.1210/clinem/dgae005

Rouault, P., Guimbal, S., Cornuault, L., Bourguignon, C., Foussard, N., Alzieu, P., et al. (2023). Thrombosis in the coronary microvasculature impairs cardiac relaxation and induces diastolic dysfunction. *ARTERIOSCLEROSIS THROMBOSIS Vasc. Biol.* 44 (1), e1–e18. doi:10.1161/ATVBAHA.123.320040

Shabab, S., Mahmoudabady, M., Gholamnezhad, Z., Fouladi, M., and Asghari, A. A. (2023). Diabetic cardiomyopathy in rats was attenuated by endurance exercise through the inhibition of inflammation and apoptosis. *Heliyon* 10 (1), e23427. doi:10.1016/j.heliyon.2023.e23427

Sousa, S., Pereira, A. M., and Santiago, L. M. (2024). Patient-centered medicine and self-care of patients with type 2 diabetes: a cross-sectional study. *Acta Medica Port.* 37 (1), 3–9. doi:10.20344/amp.18584

Sun, Z.-J., Tian, Z., Xu, T., Wang, Z. M., Zhu, X. H., Luo, J., et al. (2024). Pelvic floor muscle strength and influencing factors based on vaginal manometry among healthy women at different life stages: a multicentre cross-sectional study. *BJOG-AN Int. J. OBSTETRICS Gynaecol.* 131, 952–960. doi:10.1111/1471-0528.17736

Tayebi, S. M., Nouri, A. H., Tartibian, B., Ahmadabadi, S., Basereh, A., and Jamhiri, I. (2024). Effects of swimming training in hot and cold temperatures combined with cinnamon supplementation on HbA1C levels, TBC1D1, and TBC1D4 in diabetic rats. *Nutr. & diabetes* 14 (1), 1. doi:10.1038/s41387-023-00256-0

Wagner, K. A., Laurent, St, Christine, W., Pekow, P., Desrosiers, T., Misra, R., et al. (2023). The impact of a lifestyle intervention on postpartum cardiometabolic risk factors among hispanic women with abnormal glucose tolerance during pregnancy: secondary analysis of a randomized trial. *J. Phys. Activity & Health* 21 (1), 40–50. doi:10.1123/jpah.2023-0145

Wang, X., Wang, Y., Hou, J., Liu, H., Zeng, R., Li, X., et al. (2024). Plasma proteome profiling reveals the therapeutic effects of the PPAR pan-agonist chiglitazar on insulin sensitivity, lipid metabolism, and inflammation in type 2 diabetes. *Sci. Rep.* 14 (1), 638. doi:10.1038/s41598-024-51210-8

Yang, J., Cheng, Z., Zhang, D., Zheng, T., Yin, C., Liu, S., et al. (2023). A nested case-control study of serum zinc and incident diabetes among Chinese adults: effect modifications and mediation analysis. *Sci. TOTAL Environ.* 910, 168678. doi:10.1016/j.scitotenv.2023.168678

Yu, L., Wang, J., Gong, Q., Chen, F., Chen, Y., Li, X., et al. (2024). Influence of a diet and/or exercise intervention on long-term mortality and vascular complications in people with impaired glucose tolerance: da Qing Diabetes Prevention Outcome study. *DIABETES Obes. & METABOLISM* 26, 1188–1196. doi:10.1111/dom.15413

Zeng, Yu, Zhang, X., Luo, W., and Sheng, Y. (2024). Effect of exercise intervention on clinical parameters in patients with non-alcoholic fatty liver disease and type 2 diabetes mellitus: a meta-analysis of randomized controlled trials. *Eur. J. GASTROENTEROLOGY & HEPATOLOGY* 36 (1), 1–12. doi:10.1097/MEG.0000000000002662

Zhang, Bo, Cheng, Z., Chen, Ji, Zhang, X., Liu, D., Jiang, H., et al. (2024a). Efficacy and safety of mazdutide in Chinese patients with type 2 diabetes: a randomized, double-blind, placebo-controlled phase 2 trial. *DIABETES CARE* 47 (1), 160–168. doi:10.2337/dc23-1287

Zhang, J., Tam, W. W. S., Kanokwan, H., Kusuyama, J., and Wu, V. X. (2024b). Response to Letter to the Editor on "Effectiveness of combined aerobic and resistance exercise on cognition, metabolic health, physical function, and health-related quality of life in middle-aged and older adults with type 2 Diabetes Mellitus: a Systematic Review and Meta-Analysis. *ARCHIVES Phys. Med. REHABILITATION* 105, 1023–1024. doi:10.1016/j.apmr.2024.01.001

Zhang, Y., Wang, L., Wu, W., Zhang, S., Zhang, M., She, W., et al. (2023). Predictors of inadequate bowel preparation in older patients undergoing colonoscopy: a systematic review and meta-analysis. *Int. J. Nurs. Stud.* 149, 104631. doi:10.1016/j.ijnurstu.2023.104631

Zhu, Y., Liu, W., and Qi, Z. (2023). Adipose tissue browning and thermogenesis under physiologically energetic challenges: a remodelled thermogenic system. *J. PHYSIOLOGY-LONDON* 602 (1), 23–48. doi:10.1113/JP285269

Zimmer, R. T., Birnbaumer, P., Sternad, C., Zunner, B. E. M., Schierbauer, J., Fritsch, M., et al. (2023). Impact of a 4-week intensive track and field training intervention on glycaemia in adolescents with type 1 diabetes: the ChilDFiT1 study. *DIABETES Obes. & METABOLISM* 26 (2), 631–641. doi:10.1111/dom.15352

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Impact of diverse aerobic exercise plans on glycemic control, lipid levels, and functional activity in stroke patients with type 2 diabetes mellitus

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Aims: This study aimed to assess the effects of Low-to-Moderate Intensity Continuous Training (LMICT), Moderate-Intensity Interval Training (MIIT), and Reduced-Exertion High-Intensity Training (REHIT) on blood glucose regulation, functional recovery, and lipid levels in individuals who have experienced a stroke and are diagnosed with Type 2 Diabetes Mellitus (T2DM).

Methods: Forty-two T2DM stroke patients were randomly allocated to four groups: LMICT, MIIT, REHIT, and a control group (CON). Participants continuously monitored their blood glucose levels throughout the intervention using continuous glucose monitoring (CGM) devices. The study comprised two exercise intervention cycles: the first lasting from Day 3 to Day 14 and the second from Day 15 to Day 28, with the initial two days serving as contrasting periods. Primary outcomes encompassed CGM-derived blood glucose measurements, the Barthel Index (BI), Fugl-Meyer Assessment lower-extremity subscale (FMA-LE), and alterations in triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-c), and low-density lipoprotein cholesterol (LDL-c).

Results: Compared with the CON, the MIIT group showed significant improvements in mean glucose (MG), glucose standard deviation (SD), time above range (TAR), and time in range (TIR). The REHIT group exhibited significantly reduced time below range (TBR), glucose SD, and coefficient of variation (CV). Regarding lipid levels, although the REHIT group achieved a significant reduction in TG levels compared with the CON, the overall effects of LMICT, MIIT, and REHIT on lipid profiles were relatively modest. Concerning functional recovery, the REHIT group significantly improved the BI and FMA-LE.

Conclusion: Although the short-term quantitative impact of exercise on lipid levels may be limited, both REHIT and MIIT significantly improved glycemic management and reduced glucose variability in post-stroke patients with Type 2 Diabetes Mellitus. Additionally, REHIT notably enhanced functional recovery.

KEYWORDS

stroke, type 2 diabetes mellitus, aerobic exercise training, continuous glucose monitoring, glycemic variability, functional activity, lipid levels

1 Introduction

Stroke is a leading cause of mortality among Chinese residents, accounting for one-third of global stroke-related fatalities and representing a significant challenge to China's public health system (1, 2). Abnormal blood glucose levels have been identified as a significant risk factor for stroke, not only increasing disease complexity but also amplifying management challenges (3–5). In China, approximately 68.7% of stroke patients demonstrate glucose metabolism abnormalities, with 42.3% being concurrently diagnosed with diabetes (6). This proportion underscores the prevalence of diabetes among stroke patients and its potential impact on patient outcomes.

Glycated hemoglobin (HbA_{1c}) has been the primary target for the clinical management of hyperglycemia in patients with type 2 diabetes mellitus (T2DM), reflecting mean glucose (MG) levels over the past two to three months. However, its correlation with stroke recurrence risk appears limited. The effectiveness of intensified blood glucose control (i.e., $HbA_{1c} \leq 7\%$) in preventing recurrent strokes remains unclear for patients with diabetes in the post-acute phase (7). This ambiguity likely arises from the close association between elevated MG levels and microvascular complications of diabetes, while the association with macrovascular complications seems more indirect (8). Additionally, HbA_{1c} cannot capture blood glucose fluctuations or provide information about glucose dynamics. However, advancements in continuous glucose monitoring (CGM) technology allow for a more precise assessment of an individual's blood glucose status, offering real-time data on fluctuations, hyperglycemia, hypoglycemia, and overall glucose variability—crucial factors for diabetes treatment (9–11). Research demonstrates a clear association between time in range (TIR), time below range (TBR), and the risk of cardiovascular and cerebrovascular diseases in patients with diabetes (10, 12). Furthermore, prospective and retrospective cohort studies reveal a dose-response relationship between glycemic variability and stroke risk, emphasizing the practical significance of evaluating blood glucose levels in stroke patients using CGM-derived glycemic management indicators (13).

Effective blood glucose management is essential for the functional recovery of stroke patients, as it promotes neurovascular repair and functional improvement (14). Aerobic exercise has been established as a powerful secondary prevention strategy, reducing cardiovascular risks for post-stroke patients and managing complications associated with diabetes (15–18). The current guidelines from the American Heart Association/American Stroke Association recommend that stroke survivors engage in Low-to-Moderate Intensity Continuous Training (LMICT) three to five times per week, with each session lasting 20 to 60 minutes at an intensity of 40% to 70% of heart rate reserve, including five to ten minutes of lower-intensity warm-up and cool-down activities (19). Moreover, the American College of Sports Medicine and the American Diabetes Association recommend that patients with T2DM participate in at least 150 minutes of moderate-intensity or 75 minutes of high-intensity exercise weekly (20). However, physical disabilities frequently hinder stroke patients' ability to adhere to these exercise recommendations. This situation can impede functional recovery and potentially increase the risk of stroke recurrence due to inadequate blood sugar control (18).

Although Reduced-Exertion High-Intensity Training (REHIT) and Moderate-Intensity Interval Training (MIIT) have shown promise in improving insulin sensitivity and reducing blood glucose levels in non-stroke populations, their effects on individuals with concurrent stroke and diabetes have not been extensively explored (21, 22). Therefore, this study aims to investigate the effects of LMICT, MIIT, and REHIT on CGM-derived indicators in stroke patients with diabetes while also tracking changes in essential prognostic indicators, such as lipid levels and functional activity. Additionally, the study examines the influence of different intensity levels and compares intermittent versus continuous exercise modalities in this high-risk population. The ultimate goal is to provide clinical evidence supporting the implementation of aerobic training programs for stroke patients with diabetes, facilitating improved glycemic control, lipid management, and functional recovery.

2 Materials and methods

2.1 Study participants

The trial enrolled 42 hospitalized patients concurrently diagnosed with stroke and T2DM. All participants provided written informed consent, and the study received approval from the regional Ethics Committee. The trial has been registered with the Chinese Clinical Trial Registry. Participant selection was based

on the '2019 Diagnostic Essentials of Cerebrovascular Diseases in China' for stroke (confirmed by imaging) and the '2020 Chinese Guidelines for Type 2 Diabetes'. Inclusion criteria included age 18-80 years, a stroke occurring between 15 days to 1 year prior, the ability to walk 10 meters independently (with or without assistance), and adequate cognitive function to engage in study activities. Exclusion criteria were: unstable vital signs, progressive or acute-phase stroke, transient ischemic attacks, history of brain injury or other central nervous system issues, major cardiac or pulmonary diseases, severe hepatic or renal dysfunction, musculoskeletal limitations, untreated deep venous thrombosis, severe diabetic complications, other serious concurrent illnesses, or involvement in other clinical trials.

2.2 Study design

This prospective, randomized, controlled trial was conducted at the Rehabilitation Department of the Second People's Hospital of Shenzhen in Guangdong Province between October 2022 and October 2023. At baseline, participants underwent a comprehensive assessment, including blood tests, physiological measurements, functional evaluations, and exercise stress testing. Following the baseline assessments, 42 participants were randomly allocated to four groups: three experimental groups and one control group. The participants then engaged in a 4-week intervention trial (Figure 1). The randomization process involved participants selecting and opening opaque sealed envelopes, each containing a specific intervention assignment. The first two days of the study were designated as the "Contrast Days," and the data collected during this period were analyzed using mean values. "Cycle 1" referred to the period from day 3 to day 14, while "Cycle 2" encompassed the period from day 15 to day 28. Data analysis for these cycles was based on the mean values collected (Figure 2).

2.3 Sample size estimation

Metcalfe et al. reported that REHIT significantly reduced MG levels in patients with T2DM compared with a no-exercise control group, demonstrating a statistically significant Cohen's *d* value of 0.55 (23). Their study employed a repeated measures design with three distinct phases: baseline Contrast Days (days 1-2), Cycle 1 (days 3-14), and Cycle 2 (days 15-28). In the current study, we transformed Cohen's *d* to Cohen's *f* using the approximate transformation $f = d/2$ (24), yielding a value of 0.275. To ensure a robust sample size while accounting for variability, we set the effect size at a relatively low-medium range ($f = 0.25$). The sample size was calculated using G*Power 3.1.9.7 software (Heinrich Heine Universität Düsseldorf, Düsseldorf, Germany), indicating that a total of 40 patients would be required to achieve 80% power at a significance level of 0.05. Given the small sample size, efforts will be made to minimize attrition. This study design enables the accurate assessment of the effects of LMICT, MIIT, and REHIT on glucose control in stroke patients with T2DM and the exploration of secondary outcomes related to functional recovery and lipid levels.

2.4 Collection of primary data

Critical clinical data collected included age, gender, height, weight, the duration of diabetes, the date of stroke onset, histories of smoking and alcohol consumption, medication use, and overall medical history. During baseline and endpoint assessments, participants provided fasting ante-cubital venous blood samples for the evaluation of fasting plasma glucose (FPG), glycated hemoglobin (HbA_{1c}triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-c), and low-density lipoprotein cholesterol (LDL-c). The glucose oxidase method was employed to quantitatively assess blood glucose concentration, while the scatter turbidity method was used to measure HbA_{1c} levels, with all samples analyzed in duplicate.

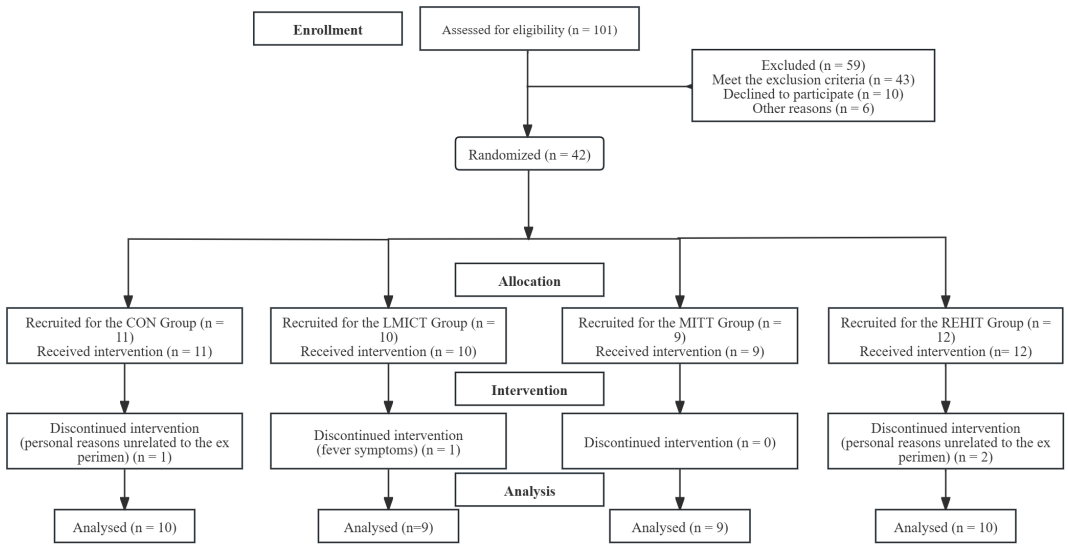

FIGURE 1
Flow diagram of the study participants.

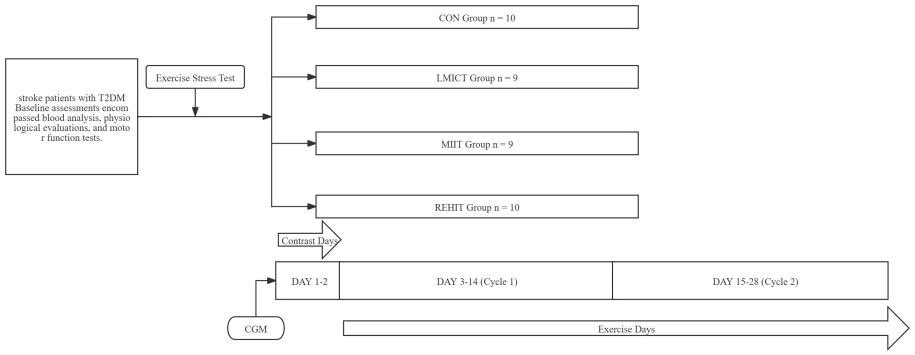

FIGURE 2
Study overview.

Furthermore, the BI was utilized to evaluate patients' activities of daily living, and the Fugl-Meyer Assessment lower-extremity subscale (FMA-LE) was administered to assess lower limb function.

2.5 Exercise stress test

In this study, participants underwent a symptom-limited maximum incremental cardiopulmonary exercise test using a four-limb coordinated rehabilitation training device (HNT-LE-E001A, Humaneutec, Guangzhou, China) and a cardiopulmonary exercise test system (Masterscreen CPX, ERGOLINE GMBH, Germany). Prior to testing, each participant was fitted with a 5-lead electrocardiogram (ECG), equipped with an automatic blood pressure monitoring cuff and a gas analysis mask, and the system was calibrated accordingly. Resistance was increased stepwise by 1-2 levels every 2 minutes based on the patient's gender, age, height, weight, functional status, and exercise habits. The test protocol comprised several phases: 1)a 1-minute resting phase, during which the patient's heart rate and blood pressure were recorded; 2) a 3-minute warm-up without resistance; 3) a load phase, during which resistance was gradually increased according to the pre-selected scheme, lasting for 8-12 minutes until either maximum exercise load was reached or termination criteria were met; 4) a recovery phase, consisting of 3 minutes of unloaded movement, followed by 3 minutes of rest, during which the recovery of blood pressure and heart rate was monitored. Each resistance level was maintained for 2 minutes throughout the exercise, with a constant pedaling speed of 80 steps/min (25). Termination criteria included: achieving a VO_2 plateau (26); a heart rate exceeding 90% of the age-predicted maximum heart rate (or 85% for those on β-blockers) (27); a respiratory exchange ratio exceeding 1.0 (28); or a Borg scale rating (6–20) exceeding 17 (29). The test was also concluded if participants could not maintain the predetermined pedaling speed despite maximal effort.

2.6 Continuous glucose monitoring

In 2017, the International Conference on Advanced Technologies & Treatments for Diabetes (ATTD) established an international consensus stating that CGM should be conducted for a duration exceeding 14 days, with at least 10 days of valid data (30). Adhering to this consensus enables more effective monitoring of trends in participant blood glucose levels. Consequently, CGM occurred throughout the 28-day intervention period, and data were segmented into three stages for trend analysis: days 1-2, days 3-14, and days 15-28. On days 0 and day 14 of the experiment, participants had glucose sensors (GS1, SIBIONICS, Shenzhen, Guangdong, China) implanted in their non-dominant upper arm, each with a lifespan of 14 days. These sensors continuously recorded glucose levels every 5 minutes to obtain the MG, TIR, TBR, and TAR for each phase. Conventional analysis methods were employed to evaluate glycemic variability, constructing coefficients of variation (CV) and the standard deviation of glucose (SD glucose) based on the statistical characteristics of previous studies.

2.7 Medication therapy and dietary plan

All participants adhered to the endocrinologist's recommendations for the administration of hypoglycemic medications. During the study, participants were directed to maintain their hypoglycemic treatment regimen without modifications, and the timing of hypoglycemic medications or insulin injections remained consistent on a daily basis. Regarding dietary intake, the caloric content and the proportions of carbohydrates, proteins, and fats in each meal were recorded for the two days preceding the experiment, referred to as the Contrast Days, based on a standardized meal plan. Under the guidance of therapists, participants were instructed to maintain the dietary patterns established during the Contrast Days for the following 22 days.

2.8 Exercise intervention program

Under strict professional supervision, all exercise interventions were conducted to ensure their safety and efficacy. Participants in the experimental group used a standardized four-limb coordinated rehabilitation training device. Based on initial cardiopulmonary

exercise test results, therapists customized the apparatus's resistance levels and pedal speeds for each participant. Continuous heart rate monitoring was implemented throughout each session to maintain optimal exercise intensity, and participants rated their perceived exertion using the Borg scale (range 6-20) immediately after each session. The exercise intervention program started on day 3 and lasted until day 24, with daily sessions. The program included two rest days after every five consecutive exercise days to prevent overtraining, resulting in 20 sessions across the intervention period. The sessions were divided into two phases, each comprising 10 sessions. Participants in the control group (CON) continued their routine treatment regimen without participating in any structured exercise program (Figure 3).

2.9 Statistics

Data were analyzed using SPSS 23 software (IBM Corporation, Armonk, NY, USA). Categorical variables were presented as percentages, and continuous variables as mean ± standard deviation (M ± SD). Differences in baseline characteristics among the CON, LMICT, MIIT, and REHIT groups were evaluated using one-way analysis of variance (ANOVA) and the chi-square test. Levene's test was applied to assess the homogeneity of variances, and if this assumption was violated, Welch's ANOVA was used. Fisher's exact test was employed for categorical variables when expected frequencies were less than five. Time and exercise mode were factors in a two-way repeated measures ANOVA for comparing and analyzing CGM data and deriving blood glucose indices for each exercise regimen. The Greenhouse-Geisser correction was applied when the assumption of sphericity was violated. Significant interaction effects were further analyzed using the Bonferroni method for pairwise comparisons. Additionally, the effects of the LMICT, MIIT, and REHIT exercise regimens on functional activity and lipid levels were assessed *via* analysis of covariance (ANCOVA), incorporating baseline TG, TC, HDL-c, LDL-c, BI, and FMA-LE as covariates, with Bonferroni correction for all pairwise comparisons. The significance level was set at $p < 0.05$.

3 Results

The study initially included 42 participants, distributed as follows: 11 in the CON group, 10 in the LMICT group, 9 in the MIIT group, and 12 in the REHIT group. Due to personal reasons unrelated to the experiment, 3 participants withdrew from the study, including one from the CON group and two from the REHIT group. Additionally, 1 participant from the LMICT group was excluded due to fever symptoms, rendering them unable to continue with the training. No participants reported adverse reactions during the LMICT, MIIT, and REHIT training sessions.

3.1 Participant characteristics

Table 1 presents the participant characteristics. No statistically significant differences were observed among the LMICT, MIIT, REHIT, and CON groups in baseline characteristics, including age, height, weight, duration of diabetes, type of stroke, days post-stroke, glucose and lipid metabolism parameters, comorbid conditions, functional activity indicators, and types of concomitant treatments, such as oral hypoglycemic agents, insulin, statins, and β1-blockers.

3.2 analysis of continuous glucose monitoring data on contrast days in cycle 1 and cycle 2

The analysis of MG values indicated a significant main effect among groups ($F = 3.110$, $p = 0.039$), while the main effect of time was not statistically significant ($F = 3.327$, $p = 0.065$). However, a significant interaction between group and time was observed ($F = 3.769$, $p = 0.011$). Specifically, in the MIIT group, MG values showed a significant reduction over time ($F = 8.343$, $p = 0.001$). Multiple comparisons demonstrated that MG values significantly decreased from Contrast Days to Cycle 1 and Cycle 2. Relative to the

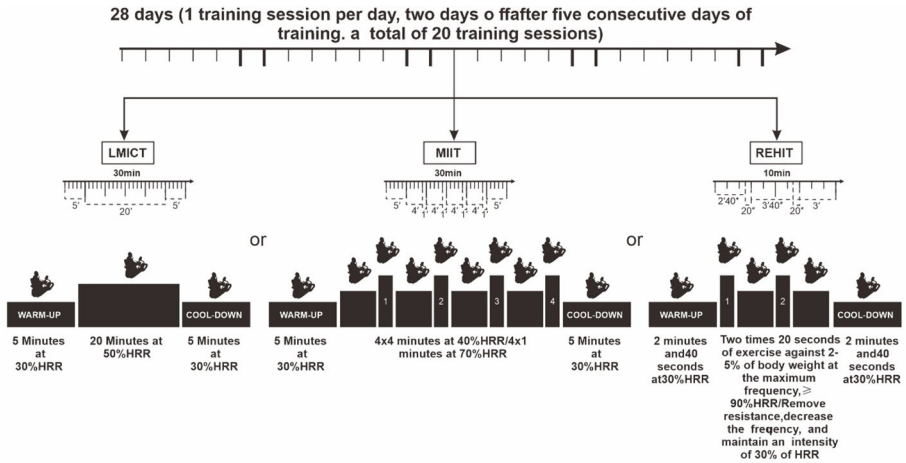

FIGURE 3
Exercise intervention program.

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TABLE 1 Demographic and baseline clinical characteristics.

	CON (n = 11)	LMICT (n = 10)	MIIT (n = 9)	REHIT (n = 12)	*P*
Withdraw halfway, n (%)	1 (9.1%)	1 (10%)	0 (0%)	2 (16.7%)	0.894
Male/female, n (%)	3 (27.3%)	1 (10.0%)	4 (44.4%)	3 (25.0%)	0.426
Age (years)	59.73 ± 12.19	62.20 ± 8.01	63.67 ± 10.28	57.42 ± 10.47	0.536
Height (cm)	166.82 ± 5.88	166.70 ± 4.37	162.56 ± 8.65	165.08 ± 8.12	0.598
Weight (kg)	63.27 ± 8.64	61.70 ± 9.88	58.33 ± 9.64	63.75 ± 9.18	0.571
Duration of diabetes >10 years, n (%)	5 (45.5%)	4 (40.0%)	6 (66.7%)	5 (41.7%)	0.675
HbA1c (%)	8.11 ± 1.57	7.52 ± 1.17	8.35 ± 1.57	7.70 ± 1.33	0.550
FBG (mmol/L)	6.46 ± 1.48	6.07 ± 1.14	7.23 ± 1.97	6.30 ± 1.16	0.523
Days since stroke onset	65.27 ± 65.41	100.00 ± 76.93	102.3 ± 101.86	121.67 ± 90.98	0.461
Ischemic stroke, n (%)	10 (90.9%)	7 (70.0%)	8 (88.9%)	9 (75.0%)	0.580
History of stroke, n (%)	2 (18.2%)	0 (0.0%)	2 (22.2%)	2 (16.7%)	0.561
With hypertension, n (%)	10 (90.9%)	9 (90.0%)	9 (100%)	12 (100.0%)	0.707
With dyslipidemia, n (%)	1 (9.1%)	1 (10.0%)	1 (11.1%)	2 (16.7%)	1.000
With coronary artery disease, n (%)	1 (9.1%)	2 (20.0%)	3 (33.3%)	2 (16.7%)	0.603
History of smoking, n (%)	4 (36.4%)	6 (60.0%)	3 (33.3%)	4 (33.3%)	0.598
History of alcohol consumption, n (%)	2 (18.2%)	5 (50.0%)	1 (11.1%)	6 (50.0%)	0.126
TG (mmol/L)	1.27 ± 0.36	1.54 ± 0.92	1.38 ± 0.57	1.10 ± 0.30	0.323
TC (mmol/L)	3.27 ± 1.24	3.27 ± 0.91	3.95 ± 1.14	3.53 ± 0.89	0.453
HDL-c (mmol/L)	0.97 ± 0.45	1.00 ± 0.23	1.07 ± 0.30	1.16 ± 0.22	0.491
LDL-c (mmol/L)	1.84 ± 0.61	1.91 ± 0.58	2.49 ± 1.00	1.99 ± 0.60	0.189
BI	58.18 ± 33.26	53.00 ± 17.19	55.00 ± 22.91	57.92 ± 22.00	0.938
FMA-LE	17.91 ± 7.78	17.60 ± 7.85	17.67 ± 7.07	18.83 ± 8.04	0.980
Oral blood-glucose-lowering medication					
Biguanides, n (%)	5 (45.5%)	5 (50.0%)	4 (44.4%)	8 (66.7%)	0.730
DPP-4 Inhibitors, n (%)	2 (18.2%)	3 (30%)	3 (33.3%)	3 (25.0%)	0.900
SGLT2 Inhibitors, n (%)	2 (18.2%)	2 (20.0%)	3 (33.3%)	2 (16.7%)	0.848
Sulfonylureas, n (%)	3 (27.3%)	4 (40.0%)	3 (33.3%)	5 (41.7%)	0.919
Insulin treatment n (%)					
Basal Insulin, n (%)	3 (27.3%)	2 (20.0%)	3 (33.3%)	3 (25.0%)	0.963
Multiple Daily Injections, n (%)	3 (27.3%)	2 (28.6%)	3 (33.3%)	2 (16.7%)	0.831
Biphasic Insulin, n (%)	1 (9.1%)	1 (10.0%)	0 (0.0%)	1 (8.3%)	1.000
Statins, n (%)	10 (90.9%)	6 (60.0%)	6 (66.7%)	8 (66.7%)	0.402
β1-blocker, n (%)	2 (18.2%)	4 (40.0%)	2 (22.2%)	4 (33.3%)	0.722

Nominal data are presented as n (%). There were no between-group differences at baseline.

Contrast Days, significant differences were observed between Cycle 1 [mean difference (MD) = -0.923, $p = 0.013$] and Cycle 2 (MD = -1.484, $p = 0.001$) (Table 2, Figure 4).

Regarding TIR values, while the main effect among groups was not significant ($F = 1.851$, $p = 0.157$), a significant main effect of time was detected ($F = 9.297$, $p = 0.002$), along with a significant interaction effect observed between time and group ($F = 3.372$, $p = 0.016$). In the MIIT group, TIR values increased significantly over time ($F = 8.947$, $p = 0.001$). Multiple comparisons indicated significant increases in TIR values from Contrast Days to Cycle 1 (MD = 13.151, $p = 0.002$) and Cycle 2 (MD = 18.771, $p < 0.001$) (Table 2, Figure 4).

The analysis of TBR values indicated that the main effect among groups was not significant ($F = 1.083$, $p = 0.370$), but the main effect of time proved significant ($F = 4.656$, $p = 0.030$), with no significant interaction between the group and time ($F = 1.598$, $p = 0.197$). In the REHIT group, TBR values significantly decreased over time ($F = 4.625$, $p = 0.017$). Multiple comparisons revealed significant reductions in TBR values from Contrast Days to Cycle 1 (MD = -3.238, $p = 0.017$) and Cycle 2 (MD = -3.912, $p = 0.012$) (Table 2, Figure 4).

The analysis of TAR values indicated that the main effect among groups was not significant ($F = 2.421$, $p = 0.083$), but the main effect of time proved significant ($F = 5.674$, $p = 0.013$), alongside a significant interaction effect observed between time and group ($F = 3.024$, $p = 0.026$). In the MIIT group, TAR values showed a significant decline over time ($F = 7.803$, $p = 0.002$). Multiple comparisons showed significant decreases in TAR values from Contrast Days to Cycle 1 (MD = -11.902, $p = 0.005$) and Cycle 2 (MD = -17.958, $p = 0.001$) (Table 2, Figure 4).

The analysis of the SD glucose indicated no significant main effect among groups ($F = 0.485$, $p = 0.695$), but the main effect of time was significant ($F = 16.737$, $p < 0.001$), with a significant interaction effect observed between time and group ($F = 4.199$, $p = 0.004$). Specifically, significant reductions in SD glucose over time were observed in the CON, MIIT, and REHIT groups ($F = 5.970$, $p = 0.006$; $F = 13.884$, $p < 0.001$; and $F = 5.789$, $p = 0.007$, respectively). Moreover, multiple comparisons revealed that in the CON condition, SD glucose significantly increased from Cycle 1 to Cycle 2 (MD = 0.271, $p = 0.004$), while in the MIIT group, SD glucose significantly decreased from Contrast Days

TABLE 2 Comparison of CGM-derived blood glucose monitoring data among participants on contrast days, cycle 1, and cycle 2.

		MG (mmol/L)	CV (%)	SD glucose (mmol/L)	TIR (%)	TBR (%)	TAR (%)
A: CON	Contrast Days	8.45 ± 1.44	27.32 ± 9.92	2.34 ± 0.96	72.61 ± 20.12	1.86 ± 3.96	25.54 ± 19.52
	Cycle 1	8.42 ± 1.55	25.74 ± 7.04	2.17 ± 0.68	74.46 ± 19.03	0.94 ± 1.08	24.61 ± 19.18
	Cycle 2	8.61 ± 1.52	28.00 ± 6.21	2.44 ± 0.76	73.37 ± 21.09	1.03 ± 1.52	25.60 ± 21.02
B: LMICT	Contrast Days	7.55 ± 0.95	30.56 ± 6.47	2.34 ± 0.66	83.21 ± 10.71	1.10 ± 1.48	15.69 ± 9.83
	Cycle 1	7.70 ± 0.72	27.80 ± 5.60	2.14 ± 0.50	82.22 ± 8.76	1.01 ± 0.96	16.77 ± 8.57
	Cycle 2	7.75 ± 0.73	26.98 ± 6.46	2.11 ± 0.61	83.57 ± 9.10	1.17 ± 1.20	15.26 ± 8.39
C: MIIT	Contrast Days	8.45 ± 2.32	29.93 ± 9.66	2.53 ± 0.97	70.51 ± 26.03	3.19 ± 3.53	26.31 ± 27.18
	Cycle 1	7.53 ± 1.01	26.44 ± 5.57	2.01 ± 0.55	83.66 ± 10.41	1.94 ± 2.00	14.40 ± 10.14
	Cycle 2	6.96 ± 0.64	25.61 ± 5.52	1.80 ± 0.46	89.28 ± 6.48	2.38 ± 1.90	8.35 ± 6.10
D: REHIT	Contrast Days	7.11 ± 1.26	31.80 ± 6.40	2.24 ± 0.45	82.39 ± 11.41	5.58 ± 8.70	12.04 ± 10.38
	Cycle 1	7.03 ± 0.76	27.83 ± 5.95	1.95 ± 0.43	88.20 ± 8.44	2.34 ± 4.31	9.46 ± 7.17
	Cycle 2	6.77 ± 0.56	26.56 ± 4.46	1.80 ± 0.37	91.04 ± 5.88	1.66 ± 2.23	7.29 ± 4.59
Between-group comparison	*F*, *P*	3.110, 0.039	0.174, 0.913	0.485, 0.695	1.851, 0.157	1.083, 0.370	2.421, 0.083
Within-subject comparison	*F*, *P*	3.327, 0.065	10.514, < 0.001	16.737, < 0.001	9.297, 0.002	4.656, 0.030	5.674, 0.013
Interaction effect	*F*, *P*	3.769, 0.011	1.577, 0.187	4.199, 0.004	3.372, 0.016	1.598, 0.197	3.024, 0.026

to Cycle 1 (MD = -0.516, p = 0.004) and Cycle 2 (MD = -0.731, p < 0.001). In the REHIT group, SD glucose significantly decreased from Contrast Days to Cycle 2 (MD = -0.439, p = 0.008) (Table 2, Figure 4).

Finally, the analysis of the CV values revealed no significant main effect among groups (F = 0.174, p = 0.913). However, the main effect of time proved significant (F = 10.514, p < 0.001), with no significant interaction effect observed between group and time (F = 1.577, p = 0.187). In the REHIT group, CV values significantly decreased over time (F = 4.562, p = 0.018). Multiple comparisons indicated that in the REHIT group, CV values significantly decreased from Contrast Days to Cycle 2 (MD = -5.235, p = 0.013) (Table 2, Figure 4).

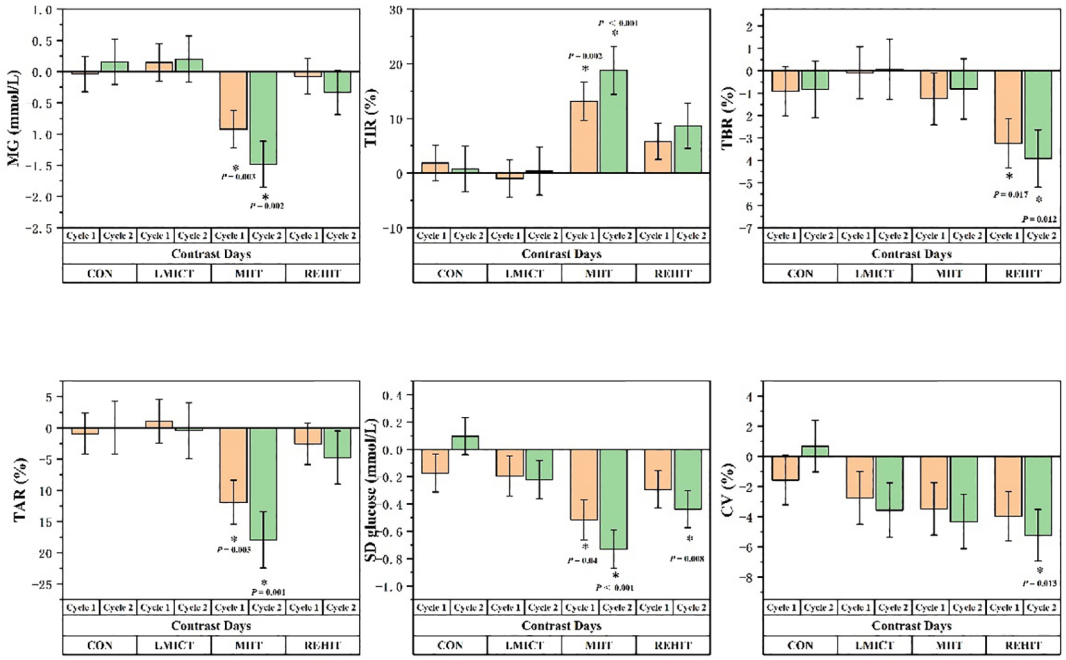

FIGURE 4
Panels display the variations in the least squares means of CGM-derived measurements relative to Contrast Days for each of Cycles 1 and 2 across the CON, LMICT, MIIT, and REHIT groups. The vertical axis depicts the difference in average values, and 'I' represents the standard error, with *$p \leq 0.05$ indicating statistical significance.

3.3 Pre- and post-study analysis of blood lipid and functional test variations

Functional outcomes, as assessed by the BI, showed mean improvements of 6.11, 8.87, 16.46, and 6.05 points in the LMICT, MIIT, REHIT, and CON groups, respectively. *Post-hoc* analyses revealed a significant improvement in the REHIT group compared with the CON group, with a least squares MD of 10.41 points (95% CI: 3.62 to 17.21, $p = 0.001$). Concurrently, FMA-LE demonstrated mean improvements of 2.43, 3.21, 4.23, and 1.20 points in the LMICT, MIIT, REHIT, and CON groups, respectively. The REHIT group exhibited a significant improvement over CON, with a least squares MD of 3.03 points (95% CI: 0.70 to 5.37, $p = 0.005$) (Table 3, Figure 5).

Throughout the study, the least squares mean of TG exhibited the following changes: it decreased by 0.13 mmol/L in the LMICT group, increased by 0.03 mmol/L in the MIIT group, decreased by 0.30 mmol/L in the REHIT group, and increased by 0.13 mmol/L in the CON group, pre- and post-study. *Post-hoc* analyses revealed that, compared to CON, the REHIT group exhibited a significant decrease in TG levels of 0.43 mmol/L (95% CI: -0.85 to -0.01, p = 0.043). The least squares mean of TC demonstrated the following changes: it increased by 0.31 mmol/L in the LMICT group, decreased by 0.01 mmol/L in the MIIT group, decreased by 0.07 mmol/L in the REHIT group, and decreased by 0.25 mmol/L in the CON group. *Post-hoc* analyses determined that changes in TC among the intervention groups, relative to the CON group, were not statistically significant. By the end of the study, the least squares mean of HDL-c shifted as follows: it declined slightly by 0.01 mmol/L in the LMICT group, increased by 0.08 mmol/L in the MIIT group, increased by 0.15 mmol/L in the REHIT group, and decreased by 0.01 mmol/L in the CON group. *Post-hoc* analyses showed no statistically significant differences in HDL-c changes between the intervention groups and the CON group. The least squares mean of LDL-c changed as follows: it decreased by 0.03 mmol/L in the LMICT group, remained stable at approximately 0.00 mmol/L in the MIIT group, decreased by 0.10 mmol/L in the REHIT group, and decreased by 0.09 mmol/L in the CON group. *Post-hoc* analyses showed no statistically significant differences in LDL-c changes between the intervention groups and CON (Table 3, Figure 4).

4 Discussion

4.1 Assessing the tolerance and safety risks of LMICT, MIIT, and REHIT in stroke patients with diabetes

This study was conducted under professional supervision, utilizing a four-limb coordinated rehabilitation training device to effectively engage significant muscle groups in accordance with guideline recommendations (31). Supervision records demonstrated an absence of adverse reactions or negative emotions during the experimental process, suggesting good tolerability of the intervention measures. Notably, inappropriate exercise can result in adverse reactions, with hypoglycemic events being the most common. Hypoglycemia may exacerbate brain damage in stroke patients, potentially leading to more severe cerebral ischemic injury, cerebral edema, and, in extreme cases, irreversible brain damage. However, this study found that the interaction effect between time and group was not significant for the LMICT, MIIT, and REHIT groups ($F = 1.598$, $p = 0.197$). No significant differences in the increase of TBR were observed between the Contrast Days, Cycle 1, and Cycle 2. Additionally, TBR values in the REHIT group significantly decreased from the Contrast Days to Cycles 1 and 2 (MD = - 3.238, $p = 0.017$; MD = -3.912, $p = 0.012$). Although research indicates that patients with T2DM treated with insulin or insulin secretagogues (such as sulfonylureas and glinides) face a higher risk of hypoglycemia after prolonged high-intensity exercise (32–36), 30 to 40 minutes of moderate-intensity exercise do not significantly raise the risk of hypoglycemia, even in those on long-term insulin therapy (37). Moreover, short-term high-intensity exercise may also help prevent hypoglycemia (20). This study corroborates previous research, suggesting that daily 30-minute sessions of LMICT, MIIT,

TABLE 3 Comparison of blood lipid and functional test indicators among participants before and after the start of the study indicators.

	CON	LMICTLMICT	MITT	REHIT
BI (number)				
Least-squares mean change ± SE between exercise day and Contrast Days	6.05 ± 1.71	6.11 ± 1.81	8.87 ± 1.80	16.46 ± 1.72
Least-squares mean difference as compared with CON (95% CI)		0.06 (-6.93; 7.05)	2.82 (-4.16; 9.80)	10.41 (3.62; 17.21)
FMA-LE (number)				
Least-squares mean change ± SE between exercise day and Contrast Days	1.20 ± 0.59	2.43 ± 0.62	3.21 ± 0.62	4.23 ± 0.59
Least-squares mean difference as compared with CON (95% CI)		1.23 (-1.17; 3.63)	2.01 (-0.39; 4.41)	3.03 (0.70; 5.37)
TG (mmol/L)				
Least-squares mean change ± SE between exercise day and Contrast Days	0.13 ± 0.11	-0.13 ± 0.11	0.03 ± 0.11	-0.30 ± 0.11
Least-squares mean difference as compared with CON (95% CI)		-0.26 (-0.70; 0.18)	-0.10 (-0.53; 0.34)	-0.43 (-0.85; -0.01)
TC (mmol/L)				
Least-squares mean change ± SE between exercise day and Contrast Days	-0.25 ± 0.16	0.31 ± 0.17	-0.01 ± 0.17	-0.07 ± 0.16
Least-squares mean difference as compared with CON (95% CI)		0.57 (-0.09; 1.22)	0.24 (-0.43; 0.92)	0.19 (-0.46; 0.83)
HDL-c (mmol/L)				
Least-squares mean change ± SE between exercise day and contrast day	-0.01 ± 0.08	-0.01 ± 0.08	0.08 ± 0.08	0.15 ± 0.08
Least-squares mean difference as compared with CON (95% CI)		0.00 (-0.31; 0.31)	0.09 (-0.23; 0.40)	0.16 (-0.16; 0.47)
LDL-c (mmol/L)				
Least-squares mean change ± SE between exercise day and Contrast Days	-0.09 ± 0.14	-0.03 ± 0.15	-0.00 ± 0.16	-0.10 ± 0.14
Least-squares mean difference as compared with CON (95% CI)		0.06 (-0.51; 0.63)	0.08 (-0.52; 0.68)	-0.01 (-0.57; 0.54)

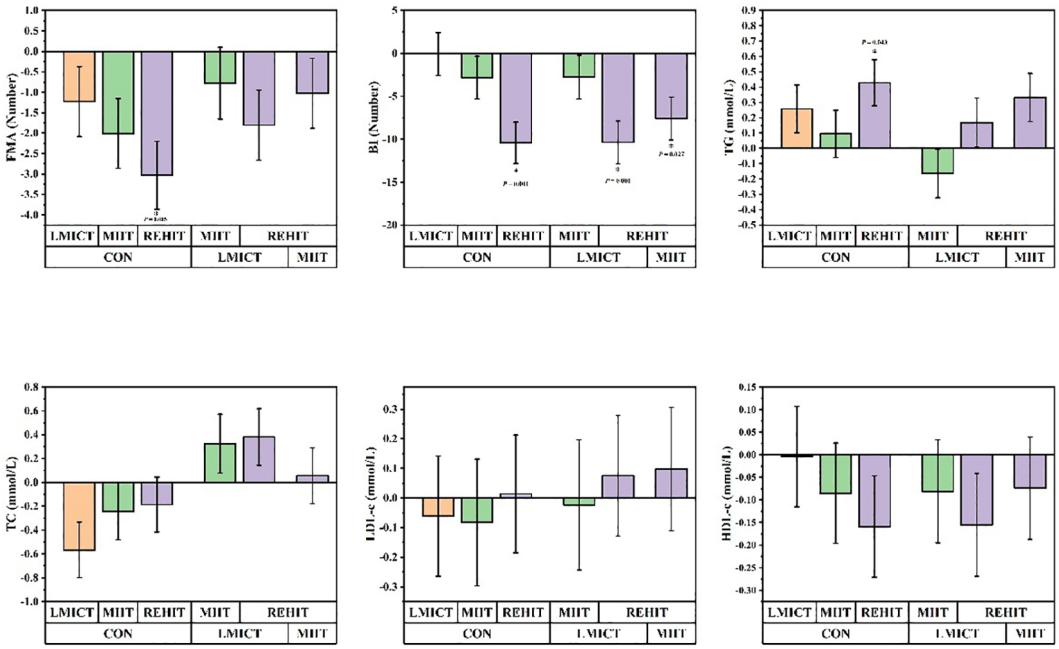

FIGURE 5
Panels display the least squares mean changes pre- and post-study for the CON group compared with the LMICT, MIIT, and REHIT groups. 'I' denotes the standard error, with *$p \leq 0.05$ denoting statistical significance.

and 10-minute sessions of REHIT do not elevate the risk of hypoglycemia in patients with concurrent diabetes and stroke.

4.2 Impact of LMICT, MIIT, and REHIT on MG levels in stroke patients with diabetes

The prevailing view holds that MG levels are the primary factor leading to the glycation of hemoglobin and other proteins, which is considered the initial stage in developing long-term complications (38, 39). This study's findings reveal a significant reduction in participants' MG levels over time under MIIT conditions. Repeated measures ANOVA demonstrated the statistical significance of MG level improvements and the critical interaction between time and exercise type, emphasizing the influence of exercise patterns and accumulated exercise days on MG levels. This finding aligns with previous research assessing the effects of 40 minutes of low-intensity continuous exercise (60% of VO_2 peak) and interval exercise (alternating 4 minutes at 50% of VO_2 peak with 1 minute at 80% of VO_2 peak) on glycated hemoglobin (HbA_{1c}) levels, noting a significant decrease in the interval exercise group. Moreover, studies have shown that long-term exercise may gradually reduce weekly HbA_{1c} levels by 0.009% to 0.043% (22, 40). Despite the close correlation between HbA_{1c} and MG levels measured by CGM, research has revealed significant variances in MG levels among individuals with identical HbA_{1c} levels, potentially due to differences in individual hemoglobin glycation rates and other physiological factors (9, 41). Consequently, MG levels have emerged as a more sensitive metric than HbA_{1c} for evaluating the effects of short-term interventions. The results of this study suggest that MIIT, which combines moderate to high intensity and duration, offers significant advantages over other exercise regimens in improving short-term average blood glucose levels in patients with diabetes and concurrent stroke.

4.3 Impact of LMICT, MIIT, and REHIT on glycemic variability in stroke patients with diabetes

At the ATTD conference, TIR was recognized as the primary metric in CGM research. Extensive research has confirmed an association between lower TIR and increased risk factors for major vascular diseases (17). A 2021 longitudinal study strongly supported TIR as a protective factor against cardiovascular disease mortality (12). Meta-analyses have indicated that exercise therapy significantly improves TIR in patients with T2DM, with a weighted mean difference (WMD) of 4.21% (95% CI: 0.95 to 7.46%; $P < 0.01$) (42). Our study further elucidates the variability in the effectiveness of different exercise regimens in enhancing TIR. Our findings indicate that, although inter-group differences in TIR were insignificant, the main effect of time was highly significant.

Furthermore, the time and exercise group interaction displayed statistical significance, with MIIT exhibiting a distinct advantage in improving TIR. Importantly, even small TIR increases of 5% have substantial clinical implications and can considerably enhance glycemic control (30). With the exception of the LMICT group, the MIIT and REHIT groups demonstrated TIR improvements, surpassing 5% from Contrast Days to Cycle 2. Correspondingly, only the MIIT group showed a statistically significant reduction in TAR from Contrast Days

to Cycle 2, potentially due to the strong inverse correlation between TIR and TAR (43). The study findings indicate that, while REHIT may have clinical significance in improving TIR among stroke patients with concurrent diabetes, MIIT is superior in decreasing hyperglycemia risk and increasing the duration patients maintain blood glucose levels within the target range. In contrast, LMICT appears ineffective in improving TIR or reducing TAR in this patient population.

4.4 Impact of LMICT, MIIT, and REHIT on glycemic variability in stroke patients with diabetes

Glycemic variability, commonly assessed using SD glucose, CV, or a combination thereof, is associated with an increased risk of recurrent cardiovascular events and mortality in patients with ischemic stroke and diabetes. Furthermore, glycemic variability is linked to brain atrophy and cognitive impairment in patients with T2DM, potentially exacerbating cognitive decline in stroke survivors (44, 45). SD glucose is a parameter reflecting daily blood glucose fluctuations, quantifying deviations from the mean level, and is a crucial indicator for assessing glycemic variability. Compared to Contrast Days, this study demonstrated a significant reduction in SD glucose for the MIIT and REHIT groups, indicating that physiological adaptations from sustained high-level exercise enhance blood glucose control. This enhancement is likely achieved by extending the duration within the target blood glucose range and minimizing the time spent at extreme glucose peaks. Compared to SD glucose, CV (calculated as SD glucose ÷MG) more accurately reflects deviations associated with hypoglycemia and significantly correlates with the TBR metric (9, 46). Although the specific mechanisms by which REHIT improves CV are not fully understood, previous research has demonstrated that 10 minutes of REHIT can reduce muscle glycogen by approximately 20% and increase the expression of peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) and glucose transporter type 4 (GLUT4) mRNA in skeletal muscle. The rapid increase in PGC-1α is associated with enhanced mitochondrial biogenesis, elevated GLUT4 expression, and increased muscle glucose transport capacity. These exercise-induced adaptive changes indicate that the upregulation of PGC-1α and GLUT4 contributes to improved glucose uptake and could enhance glucose utilization efficiency by promoting fatty acid oxidation and enhanced muscle insulin sensitivity, thereby benefiting the control or reduction of hypoglycemia risk and maintaining stable blood glucose levels (47, 48). These findings highlight the beneficial effects of MIIT and REHIT on reducing glycemic variability in patients with stroke and concurrent T2DM, with REHIT offering additional benefits in managing hypoglycemic deviations.

4.5 Impact of LMICT, MIIT, and REHIT on blood lipid profiles and functional test variations in stroke patients with diabetes

Patients who have experienced a stroke should routinely undergo lipid screenings, including TC, LDL-c, HDL-c, and TG measurements (49). Current research demonstrates that stroke patients engaged in secondary preventive medication can significantly reduce their TG levels after six weeks of regular exercise, which includes activities such as assisted walking and non-weight-bearing treadmill sessions (50). This study further revealed that after four weeks of LMICT, MIIT, and REHIT training, only the REHIT group exhibited a significant decrease in TG levels compared to the CON (least squares MD = -0.43 mmol/L, 95% CI: -0.85 to -0.01, p = 0.043). This finding is consistent with the results of Cuddy et al., who observed that REHIT significantly lowers TG levels and surpasses traditional 30-minute continuous aerobic exercises at 50%-65% heart rate reserve (HRR) (51). Although the clinical benefits of reduced TG levels in this trial remain unconfirmed, a meta-analysis of 64 studies suggests a strong association between elevated TG levels and an increased risk of stroke (adjusted relative risk [RR] 1.05; 95% CI: 1.03 to 1.07), with every 10 mg/dL increase in TG corresponding to an increase in relative risk (52). TG levels are inversely related to the risk of hemorrhagic stroke (53, 54). However, similar to most exercise trials involving patients with stroke or transient ischemic attack (TIA) (16, 55–57), changes in TC, LDL-c, and HDL-c levels in the MIIT, LMICT, and REHIT groups were not significant in this study. While reducing LDL-c is recognized as a strategy to decrease recurrent stroke risk—with potential reductions of up to 20% in the five-year risk of major vascular events per 1 mmol/L—neither MIIT, REHIT, nor LMICT achieved the MD reported in D'Isabella et al.'s meta-analysis (-0.19 mmol/L, 95% CI: -0.88 to 0.50) (16, 58). This discrepancy may arise from D'Isabella's inclusion of strength training, whereas a meta-analysis focused solely on aerobic training showed a modest post-exercise MD in LDL-c of only 0.06 mmol/L (95% CI: -0.28 to 0.15) (57), indicating the limited impact of aerobic training on LDL-c levels. Consequently, despite REHIT's positive effect on TG levels, the overall short-term quantitative effects of LMICT, MIIT, and REHIT on lipid profiles in patients with diabetes and stroke are limited.

Furthermore, this study demonstrated a strong correlation between exercise intensity and functional recovery indices, with significant improvements in the BI and FMA. This finding aligns with prior research, which suggests that aerobic training, especially at high intensities, significantly improves functional recovery in stroke patients (59, 60). As exercise intensity escalated from LMICT to MIIT and REHIT, incremental enhancements in BI and FMA-LE were noted, with particularly significant improvements observed in the REHIT group. Surpassing a clinically significant threshold of 10 BI points indicates statistical significance and clinical relevance (61). This finding underscores the advantages of higher-intensity exercise in enhancing lower limb functional recovery compared to lower-intensity exercise, reaffirming the importance of selecting an appropriate exercise intensity for stroke patients' rehabilitation.

5 Limitations of the study

Several meta-analyses published in 2020 and 2021 indicate that although numerous trials have investigated the impact of exercise on glycemic variability (GV) in patients with T2DM, systematic research on long-term training interventions (duration ≥2 weeks) remains

limited (62–64). Our comprehensive literature search further corroborates this conclusion. To our knowledge, this study represents the first to employ CGM technology to continuously monitor patients with T2DM and concurrent stroke, assessing GV, MG, and TIR during a four-week randomized controlled exercise intervention while simultaneously providing data on lipid profiles and functional recovery. Although this trial demonstrated that four weeks of exercise training positively influences glycemic fluctuations, lipid profiles, and functional recovery, additional research involving more extended training and follow-up periods is crucial to fully comprehend the persistence and effectiveness of these effects. Moreover, despite the absence of statistically significant differences in medication use among the study groups, the diverse mechanisms of action of antidiabetic drugs may influence exercise-induced changes in blood glucose. Future investigations should monitor post-exercise blood glucose variability in users of various antidiabetic drugs (including insulin) to explore the interactions between these medications and exercise training and their impact on glucose management. Finally, while this study provides novel insights for patients with diabetes and stroke, the preliminary nature of these findings, attributable to the restricted sample size, underscores the necessity for more extensive studies (20). Given the small sample size of the trial, the results should be interpreted with caution. Despite these limitations, our findings offer new perspectives on personalized exercise interventions for patients with diabetes and stroke and emphasize the need for prospective clinical trials incorporating more extended intervention and follow-up periods to validate our preliminary results.

6 Conclusions

The findings of this study demonstrate that REHIT and MIIT significantly improve glycemic control indicators for patients with T2DM following a stroke. Data collected through CGM indicate that REHIT and MIIT can effectively reduce SD glucose, thereby reducing glucose fluctuations. It is noteworthy that REHIT has demonstrated significant advantages in reducing CV and TBR, indicating its potential benefits in correcting hypoglycemic deviations. Conversely, MIIT is more effective in lowering MG, enhancing TIR, and improving TAR for high blood glucose levels. However, the efficacy of LMICT in improving CGM-measured blood glucose control indicators is relatively limited.

Furthermore, while exercise induces modest short-term effects on lipid profiles, REHIT demonstrates a more substantial decrease in triglyceride levels compared to the control group. As exercise intensity escalates, notable enhancements in BI and FMA-LE are observed, particularly within the REHIT group, underscoring the beneficial influence of exercise intensity on facilitating functional recovery. Although these findings necessitate additional research for corroboration, they provide a valuable framework for tailored exercise prescriptions for individuals with T2DM following a stroke.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Shenzhen Second People's Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

KC: Methodology, Investigation, Formal analysis, Writing – review & editing, Writing – original draft, Conceptualization. YW: Methodology, Conceptualization, Writing – review & editing. DL: Investigation, Writing – review & editing. JL: Writing – original draft. YH: Data curation, Investigation, Writing – original draft. MH: Writing – review & editing, Validation, Methodology, Formal analysis, Conceptualization. HM: Writing – review & editing, Validation, Methodology, Formal analysis, Conceptualization.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Zhou M, Wang H, Zeng X, Yin P, Zhu J, Chen W, et al. Mortality, morbidity, and risk factors in China and its provinces, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet (London England)*. (2019) 394:1145–58. doi: 10.1016/s0140-6736(19)30427-1

2. Hu G, Gu H, Jiang Y, Yang X, Wang C, Jiang Y, et al. Prevalence and In-hospital outcomes of diabetes among acute ischemic stroke patients in China: results from the Chinese Stroke Center Alliance. *J Neurol*. (2022) 269:4772–82. doi: 10.1007/s00415-022-11112-z

3. Madsen TE, Long DL, Carson AP, Howard G, Kleindorfer DO, Furie KL, et al. Sex and race differences in the risk of ischemic stroke associated with fasting blood glucose in REGARDS. *Neurology*. (2021) 97:e684–94. doi: 10.1212/wnl.0000000000012296

4. Jia Q, Liu G, Zheng H, Zhao X, Wang C, Wang Y, et al. Impaired glucose regulation predicted 1-year mortality of Chinese patients with ischemic stroke: data from abnormal glucose regulation in patients with acute stroke across China. *Stroke*. (2014) 45:1498–500. doi: 10.1161/strokeaha.113.002977

5. Tian DS, Liu CC, Wang CL, Qin C, Wang MH, Liu WH, et al. Prevalence and risk factors of stroke in China: a national serial cross-sectional study from 2003 to 2018. *Stroke Vasc Neurol*. (2023) 8:238–48. doi: 10.1136/svn-2022-001598

6. Jia Q, Zheng H, Zhao X, Wang C, Liu G, Wang Y, et al. Abnormal glucose regulation in patients with acute stroke across China: prevalence and baseline patient characteristics. *Stroke*. (2012) 43:650–7. doi: 10.1161/strokeaha.111.633784

7. Kleindorfer DO, Towfighi A, Chaturvedi S, Cockroft KM, Gutierrez J, Lombardi-Hill D, et al. 2021 Guideline for the prevention of stroke in patients with stroke and transient ischemic attack: A guideline from the american heart association/american stroke association. *Stroke*. (2021) 52:e364–467. doi: 10.1161/str.0000000000000037

8. Chehregosha H, Khamseh ME, Malek M, Hosseinpanah F, Ismail-Beigi F. A view beyond hbA1c: role of continuous glucose monitoring. *Diabetes Ther*. (2019) 10:853–63. doi: 10.1007/s13300-019-0619-1

9. Danne T, Nimri R, Battelino T, Bergenstal RM, Close KL, DeVries JH, et al. International consensus on use of continuous glucose monitoring. *Diabetes Care*. (2017) 40:1631–40. doi: 10.2337/dc17-1600

10. Yapanis M, James S, Craig ME, O'Neal D, Ekinci EI. Complications of diabetes and metrics of glycemic management derived from continuous glucose monitoring. *J Clin Endocrinol Metab*. (2022) 107:e2221–36. doi: 10.1210/clinem/dgac034

11. Garber AJ, Handelsman Y, Grunberger G, Einhorn D, Abrahamson MJ, Barzilay JI, et al. CONSENSUS STATEMENT BY THE AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY ON THE COMPREHENSIVE TYPE 2 DIABETES MANAGEMENT ALGORITHM - 2020 EXECUTIVE SUMMARY. *Endocrine Pract*. (2020) 26:107–39. doi: 10.4158/cs-2019-0472

12. Lu J, Wang C, Shen Y, Chen L, Zhang L, Cai J, et al. Time in range in relation to all-cause and cardiovascular mortality in patients with type 2 diabetes: A prospective cohort study. *Diabetes Care*. (2021) 44:549–55. doi: 10.2337/dc20-1862

13. Ren X, Wang Z, Guo C. Long-term glycemic variability and risk of stroke in patients with diabetes: a meta-analysis. *Diabetol Metab Syndrome*. (2022) 14:6. doi: 10.1186/s13098-021-00770-0

14. Prakash R, Li W, Qu Z, Johnson MA, Fagan SC, Ergul A. Vascularization pattern after ischemic stroke is different in control versus diabetic rats: relevance to stroke recovery. *Stroke*. (2013) 44:2875–82. doi: 10.1161/strokeaha.113.001660

15. Prior PL, Suskin N. Exercise for stroke prevention. *Stroke Vasc Neurol*. (2018) 3:59–68. doi: 10.1136/svn-2018-000155

16. D'Isabella NT, Shkredova DA, Richardson JA, Tang A. Effects of exercise on cardiovascular risk factors following stroke or transient ischemic attack: a systematic review and meta-analysis. *Clin Rehabilitation*. (2017) 31:1561–72. doi: 10.1177/0269215517709051

17. Serra MC, Hafer-Macko CE, Robbins R, O'Connor JC, Ryan AS. Randomization to treadmill training improves physical and metabolic health in association with declines in oxidative stress in stroke. *Arch Phys Med Rehabilitation*. (2022) 103:2077–84. doi: 10.1016/j.apmr.2022.06.011

18. Ivey FM, Ryan AS, Hafer-Macko CE, Goldberg AP, Macko RF. Treadmill aerobic training improves glucose tolerance and indices of insulin sensitivity in disabled stroke survivors: a preliminary report. *Stroke*. (2007) 38:2752–8. doi: 10.1161/strokeaha.107.490391

19. Billinger SA, Arena R, Bernhardt J, Eng JJ, Franklin BA, Johnson CM, et al. Physical activity and exercise recommendations for stroke survivors: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. (2014) 45:2532–53. doi: 10.1161/str.0000000000000022

20. Kanaley JA, Colberg SR, Corcoran MH, Malin SK, Rodriguez NR, Crespo CJ, et al. Exercise/physical activity in individuals with type 2 diabetes: A consensus statement from the american college of sports medicine. *Med Sci Sports Exercise*. (2022) 54:353–68. doi: 10.1249/mss.0000000000002800

21. Ruffino JS, Songsorn P, Haggett M, Edmonds D, Robinson AM, Thompson D, et al. A comparison of the health benefits of reduced-exertion high-intensity interval training (REHIT) and moderate-intensity walking in type 2 diabetes patients. *Appl Physiol Nutrition Metab = Physiol Appliquee Nutr Metabolisme*. (2017) 42:202–8. doi: 10.1139/apnm-2016-0497

22. Mitranun W, Deerochanawong C, Tanaka H, Suksom D. Continuous vs interval training on glycemic control and macro- and microvascular reactivity in type 2 diabetic patients. *Scand J Med Sci Sports*. (2014) 24:e69–76. doi: 10.1111/sms.12112

23. Metcalfe RS, Fitzpatrick B, Fitzpatrick S, McDermott G, Brick N, McClean C, et al. Extremely short duration interval exercise improves 24-h glycaemia in men with type 2 diabetes. *Eur J Appl Physiol*. (2018) 118:2551–62. doi: 10.1007/s00421-018-3980-2

24. Cohen J. *Statistical power analysis for the behavioral sciences*. New York: Routledge (1988).

25. Billinger SA, Tseng BY, Kluding PM. Modified total-body recumbent stepper exercise test for assessing peak oxygen consumption in people with chronic stroke. *Phys Ther*. (2008) 88:1188–95. doi: 10.2522/ptj.20080072

26. Yates JS, Studenski S, Gollub S, Whitman R, Perera S, Lai SM, et al. Bicycle ergometry in subacute-stroke survivors: feasibility, safety, and exercise performance. *J Aging Phys Activity*. (2004) 12:64–74. doi: 10.1123/japa.12.1.64

27. Mattlage AE, Ashenden AL, Lentz AA, Rippee MA, Billinger SA. Submaximal and peak cardiorespiratory response after moderate-high intensity exercise training in subacute stroke. *Cardiopulmonary Phys Ther J*. (2013) 24:14–20. doi: 10.1097/01823246-201324030-00003

28. Edvardsen E, Hem E, Anderssen SA. End criteria for reaching maximal oxygen uptake must be strict and adjusted to sex and age: a cross-sectional study. *PloS One*. (2014) 9:e85276. doi: 10.1371/journal.pone.0085276

29. Billinger SA, Vans E, McClain M, Lentz AA, Good MB. Recumbent stepper submaximal exercise test to predict peak oxygen uptake. *Med Sci Sports Exercise*. (2012) 44:1539–44. doi: 10.1249/MSS.0b013e31824f5be4

30. Battelino T, Danne T, Bergenstal RM, Amiel SA, Beck R, Biester T, et al. Clinical targets for continuous glucose monitoring data interpretation: recommendations from the international consensus on time in range. *Diabetes Care*. (2019) 42:1593–603. doi: 10.2337/dci19-0028

31. MacKay-Lyons M, Billinger SA, Eng JJ, Dromerick A, Giacomantonio N, Hafer-Macko C, et al. Aerobic exercise recommendations to optimize best practices in care after stroke: AEROBICS 2019 update. *Phys Ther*. (2020) 100:149–56. doi: 10.1093/ptj/pzz153

32. Zierath JR, He L, Gumà A, Odegoard Wahlström E, Klip A, Wallberg-Henriksson H. Insulin action on glucose transport and plasma membrane GLUT4 content in skeletal muscle from patients with NIDDM. *Diabetologia*. (1996) 39:1180–9. doi: 10.1007/bf02658504

33. Kennedy JW, Hirshman MF, Gervino EV, Ocel JV, Forse RA, Hoenig SJ, et al. Acute exercise induces GLUT4 translocation in skeletal muscle of normal human subjects and subjects with type 2 diabetes. *Diabetes*. (1999) 48:1192–7. doi: 10.2337/diabetes.48.5.1192

34. Musi N, Fujii N, Hirshman MF, Ekberg I, Fröberg S, Ljungqvist O, et al. AMP-activated protein kinase (AMPK) is activated in muscle of subjects with type 2 diabetes during exercise. *Diabetes*. (2001) 50:921–7. doi: 10.2337/diabetes.50.5.921

35. Rosenstock J, Hassman DR, Madder RD, Brazinsky SA, Farrell J, Khutoryansky N, et al. Repaglinide versus nateglinide monotherapy: a randomized, multicenter study. *Diabetes Care*. (2004) 27:1265–70. doi: 10.2337/diacare.27.6.1265

36. Larsen JJ, Dela F, Madsbad S, Vibe-Petersen J, Galbo H. Interaction of sulfonylureas and exercise on glucose homeostasis in type 2 diabetic patients. *Diabetes Care*. (1999) 22:1647–54. doi: 10.2337/diacare.22.10.1647

37. van Dijk JW, Manders RJ, Tummers K, Bonomi AG, Stehouwer CD, Hartgens F, et al. Both resistance- and endurance-type exercise reduce the prevalence of hyperglycaemia in individuals with impaired glucose tolerance and in insulin-treated and non-insulin-treated type 2 diabetic patients. *Diabetologia*. (2012) 55:1273–82. doi: 10.1007/s00125-011-2380-5

38. Ceriello A, Prattichizzo F, Phillip M, Hirsch IB, Mathieu C, Battelino T. Glycaemic management in diabetes: old and new approaches. *Lancet Diabetes Endocrinol*. (2022) 10:75–84. doi: 10.1016/s2213-8587(21)00245-x

39. El Malahi A, Van Elsen M, Charleer S, Dirinck E, Ledeganck K, Keymeulen B, et al. Relationship between time in range, glycemic variability, hbA1c, and complications in adults with type 1 diabetes mellitus. *J Clin Endocrinol Metab*. (2022) 107:e570–81. doi: 10.1210/clinem/dgab688

40. Grace A, Chan E, Giallauria F, Graham PL, Smart NA. Clinical outcomes and glycaemic responses to different aerobic exercise training intensities in type II diabetes: a systematic review and meta-analysis. *Cardiovasc Diabetol*. (2017) 16:37. doi: 10.1186/s12933-017-0518-6

41. Wilson DM, Xing D, Beck RW, Block J, Bode B, Fox LA, et al. Hemoglobin A1c and mean glucose in patients with type 1 diabetes: analysis of data from the Juvenile Diabetes Research Foundation continuous glucose monitoring randomized trial. *Diabetes Care*. (2011) 34:540–4. doi: 10.2337/dc10-1054

42. Zhu X, Zhao L, Chen J, Lin C, Lv F, Hu S, et al. The effect of physical activity on glycemic variability in patients with diabetes: A systematic review and meta-analysis of randomized controlled trials. *Front Endocrinol*. (2021) 12:767152. doi: 10.3389/fendo.2021.767152

43. Dai DJ, Lu JY, Zhang L, Shen Y, Mo YF, Lu W, et al. The appropriate cut-off point of time in range (TIR) for evaluating glucose control in type 2 diabetes mellitus.

Zhonghua yi xue za zhi. (2020) 100:2990–6. doi: 10.3760/cma.j.cn112137-20200619-01895

44. Papachristoforou E, Lambadiari V, Maratou E, Makrilakis K. Association of glycemic indices (Hyperglycemia, glucose variability, and hypoglycemia) with oxidative stress and diabetic complications. *J Diabetes Res*. (2020) 2020:7489795. doi: 10.1155/2020/7489795

45. Lee KP, Chen JS, Wang CY. Association between diabetes mellitus and post-stroke cognitive impairment. *J Diabetes Invest*. (2023) 14:6–11. doi: 10.1111/jdi.13914

46. Yoo JH, Kim JH. Time in range from continuous glucose monitoring: A novel metric for glycemic control. *Diabetes Metab J*. (2020) 44:828–39. doi: 10.4093/dmj.2020.0257

47. Benton CR, Nickerson JG, Lally J, Han XX, Holloway GP, Glatz JF, et al. Modest PGC-1alpha overexpression in muscle in *vivo* is sufficient to increase insulin sensitivity and palmitate oxidation in subsarcolemmal, not intermyofibrillar, mitochondria. *J Biol Chem*. (2008) 283:4228–40. doi: 10.1074/jbc.M704332200

48. Ren JM, Semenkovich CF, Gulve EA, Gao J, Holloszy JO. Exercise induces rapid increases in GLUT4 expression, glucose transport capacity, and insulin-stimulated glycogen storage in muscle. *J Biol Chem*. (1994) 269:14396–401. doi: 10.1016/S0021-9258(17)36636-X

49. Yaghi S, Elkind MSV. Lipids and cerebrovascular disease. *Stroke*. (2015) 46:3322–8. doi: 10.1161/STROKEAHA.115.011164

50. Palmcrantz S, Cremoux A, Kahan T, Borg J. Effects of different exercise protocols on aerobic capacity, blood pressure, biochemical parameters, and body weight in chronic stroke survivors: a randomized controlled trial. *Topics Stroke Rehabilitation*. (2024) 2:1–10. doi: 10.1080/10749357.2024.2359344

51. Cuddy TF, Ramos JS, Dalleck LC. Reduced Exertion High-Intensity Interval Training is More Effective at Improving Cardiorespiratory Fitness and Cardiometabolic Health than Traditional Moderate-Intensity Continuous Training. *Int J Environ Res Public Health*. (2019) 16(3):483. doi: 10.3390/ijerph16030483

52. Labreuche J, Deplanque D, Touboul PJ, Bruckert E, Amarenco P. Association between change in plasma triglyceride levels and risk of stroke and carotid atherosclerosis: systematic review and meta-regression analysis. *Atherosclerosis*. (2010) 212:9–15. doi: 10.1016/j.atherosclerosis.2010.02.011

53. Bonaventure A, Kurth T, Pico F, Barberger-Gateau P, Ritchie K, Stapf C, et al. Triglycerides and risk of hemorrhagic stroke vs. ischemic vascular events: The Three-City Study. *Atherosclerosis*. (2010) 210:243–8. doi: 10.1016/j.atherosclerosis.2009.10.043

54. Wieberdink RG, Poels MM, Vernooij MW, Koudstaal PJ, Hofman A, van der Lugt A, et al. Serum lipid levels and the risk of intracerebral hemorrhage: the Rotterdam Study. *Arterioscler Thromb Vasc Biol*. (2011) 31:2982–9. doi: 10.1161/atvbaha.111.234948

55. Wang C, Redgrave J, Shafizadeh M, Majid A, Kilner K, Ali AN. Aerobic exercise interventions reduce blood pressure in patients after stroke or transient ischaemic attack: a systematic review and meta-analysis. *Br J Sports Med*. (2019) 53:1515–25. doi: 10.1136/bjsports-2017-098903

56. MacKay-Lyons M, Gubitz G, Phillips S, Giacomantonio N, Firth W, Thompson K, et al. Program of rehabilitative exercise and education to avert vascular events after non-disabling stroke or transient ischemic attack (PREVENT trial): A randomized controlled trial. *Neurorehabil Neural Repair*. (2022) 36:119–30. doi: 10.1177/15459683211060345

57. Brouwer R, Wondergem R, Otten C, Pisters MF. Effect of aerobic training on vascular and metabolic risk factors for recurrent stroke: a meta-analysis. *Disabil Rehabil*. (2021) 43:2084–91. doi: 10.1080/09638288.2019.1692251

58. Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet (London England)*. (2005) 366:1267–78. doi: 10.1016/s0140-6736(05)67394-1

59. Pohl M, Werner C, Holzgraefe M, Kroczek G, Mehrholz J, Wingendorf I, et al. Repetitive locomotor training and physiotherapy improve walking and basic activities of daily living after stroke: a single-blind, randomized multicentre trial (DEutsche GAngtrainerStudie, DEGAS). *Clin Rehabilitation*. (2007) 21:17–27. doi: 10.1177/0269215506071281

60. Boyne P, Dunning K, Carl D, Gerson M, Khoury J, Kissela B. High-intensity interval training in stroke rehabilitation. *Top Stroke Rehabil*. (2013) 20:317–30. doi: 10.1310/tsr2004-317

61. Hsieh Y-W, Wang C-H, Wu S-C, Chen P-C, Sheu C-F, Hsieh C-L. Establishing the minimal clinically important difference of the barthel index in stroke patients. *Neurorehabilitation Neural Repair*. (2007) 21:233–8. doi: 10.1177/1545968306294729

62. Munan M, Oliveira CLP, Marcotte-Chénard A, Rees JL, Prado CM, Riesco E, et al. Acute and chronic effects of exercise on continuous glucose monitoring outcomes in type 2 diabetes: A meta-analysis. *Front Endocrinol*. (2020) 11:495. doi: 10.3389/fendo.2020.00495

63. Bennetsen SL, Feineis CS, Legaard GE, Lyngbæk MPP, Karstoft K, Ried-Larsen M. The impact of physical activity on glycemic variability assessed by continuous glucose monitoring in patients with type 2 diabetes mellitus: A systematic review. *Front Endocrinol*. (2020) 11:486. doi: 10.3389/fendo.2020.00486

64. Sparks JR, Kishman EE, Sarzynski MA, Davis JM, Grandjean PW, Durstine JL, et al. Glycemic variability: Importance, relationship with physical activity, and the influence of exercise. *Sports Med Health Sci*. (2021) 3:183–93. doi: 10.1016/j.smhs.2021.09.004

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Comprehensive management of gestational diabetes mellitus: practical efficacy of exercise therapy and sustained intervention strategies

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Background: Gestational Diabetes Mellitus (GDM) affects 14.0% of pregnancies globally, with a 35% post-pregnancy relapse and a 60% risk of Type 2 Diabetes (T2D) within 5-10 years. Challenges in long-term management, especially postpartum, include adherence and follow-up difficulties.

Methods: This study, based on a systematic review and meta-analysis, examined the practical effects of exercise therapy in the prevention, treatment, and prevention of progression from Gestational Diabetes Mellitus (GDM) to Type 2 Diabetes (T2D). Relevant research and clinical practices were retrieved from six major databases (PubMed, Scopus, Web of Science, Cochrane Library, MEDLINE, Science Direct). After analyzing the intervention effects of exercise therapy at different stages, factors favorably influencing the effectiveness of exercise intervention were identified during the more effective stages. Finally, a long-term and efficient exercise implementation plan for the comprehensive management of GDM was proposed.

Results: In GDM prevention, exercise reduced the post-intervention risk by 37% compared to the control group (Relative Risk (RR)=0.63; 95% Confidence Interval (CI): 0.54 to 0.72; p=0.01). Studies on GDM treatment showed improved glucose control in the exercise group post-intervention (Mean Difference (MD)=-0.10; 95% CI: -0.16 to -0.04; p=0.04/MD=-0.27; 95% CI: -0.36 to -0.19; p<0.0001). However, exercise therapy didn't significantly affect the incidence of T2D post-GDM (RR=0.88; 95% CI: 0.69 to 1.11; p=0.39) due to challenges in quantified exercise prescriptions and the complexity of postpartum programs.

Conclusion: To enhance exercise therapy effectiveness in GDM management, the study recommends adopting an integrated model emphasizing personalized pregnancy plans, postpartum strategies, and long-term support. Leveraging frequent healthcare contact during pregnancy can establish and sustain

exercise habits, fostering a lifelong pattern. While the study acknowledges limitations, this approach holds potential for improving glycemic metabolism and developing healthy exercise habits in subsequent generations. Future research should include longer follow-ups to validate the practical efficacy of this approach in preventing T2D after GDM.

Systematic review registration: https://www.crd.york.ac.uk/prospero, identifier CRD42023463617.

KEYWORDS

gestational diabetes mellitus, type 2 diabetes, exercise, lifestyle, meta-analysis

1 Introduction

Gestational Diabetes Mellitus (GDM) is a metabolic disorder that commonly occurs during pregnancy and is typically screened between weeks 24~28 through a 75g Oral Glucose Tolerance Test (OGTT). Currently, the global incidence of GDM is approximately 14.0% (95% CI: 13.97-14.04%) (1).Without intervention, GDM patients have a recurrence rate of 35% in subsequent pregnancies (95% CI, 25.5-44.5%) (2), and 60% of GDM patients may develop Type 2 Diabetes (T2D) within 5-10 years postpartum (3). Women with a history of GDM have nearly a 10-fold increased risk of developing T2D compared to those with normal glucose pregnancies (4).

Diabetes prevention programs suggest that lifestyle interventions can reduce the risk of developing T2D by 34% within 10 years (5). Lifestyle interventions, as non-pharmacological approaches, typically include exercise and dietary interventions, with exercise intervention being the most challenging to maintain. In studies on exercise therapy for preventing GDM, pregnant women demonstrate high adherence, significantly reducing the incidence of GDM (6). However, in studies on exercise therapy for treating GDM, there is often a decrease in adherence among pregnant women. Specifically, in research on exercise therapy in the post-GDM prognosis stage, only one-third of individuals engage in physical activity (7). A systematic review suggests that while physical activity can reduce the risk of T2D, exercise intervention measures in the post-GDM stage largely fail to modify their physical activity behavior (8). This suggests that the practical effectiveness of exercise intervention in post-GDM management may be less than theoretical.

The aforementioned studies on exercise therapy management of GDM collectively contribute to the comprehensive management of GDM, encompassing prevention, treatment, patient prognosis, and long-term health. To enhance the intervention effectiveness of exercise therapy in the comprehensive management of GDM, it is essential to address the issue of inadequate adherence to exercise in the post-GDM prognosis stage.

Focusing on these issues, this study aims to explore the practical effects of exercise therapy in the prevention, treatment, and prevention of GDM progression to Type 2 Diabetes. We will integrate the latest research and clinical practices, conducting meta-analyses to understand the varying intervention effects of exercise therapy in different stages of GDM –prevention, treatment, and post-prognosis. Subsequently, starting from the stages where exercise intervention shows better results, we will analyze and summarize favorable factors influencing exercise intervention effectiveness. Finally, we will discuss how to leverage these factors to improve women's adherence to exercise in the post-GDM prognosis stage, ensuring maximum health benefits. Our aim is to maximize the pivotal role of exercise therapy in managing GDM, enhancing women's metabolic health, and mitigating the risk of future T2D and other chronic diseases. We envisage offering valuable insights for the fields of obstetrics and gynecology, as well as the healthcare system at large.

2 Method

Our study protocol was registered with the PROSPERO (Registration number: CRD42023463617) and was developed according to PRISMA and the Cochrane Collaboration Handbook (9, 10).

2.1 Search strategy

Search of the PubMed, Scopus, Web of Science, Cochrane Library, MEDLINE, Science Direct (Elsevier) from inception to November 2023 for randomized controlled trials (RCTs) aimed at assessing the effect of exercise interventions on GDM and Type 2 Diabetes After GDM. We conducted searches for all relevant subject terms and free-text keywords related to exercise, randomized controlled trials, GDM, and type 2 diabetes after GDM, and then formulated search strategies based on the retrieval requirements of

different databases. See Supplementary File 1 for specific search strategies.

2.2 Inclusion and exclusion criteria

2.2.1 Inclusion criteria

Participants: Normal pregnant women (studies on GDM prevention), pregnant women with gestational diabetes mellitus (GDM) (studies on GDM treatment), or women with a history of GDM (studies on GDM prognosis). Intervention: Exercise intervention in the experimental group. Control: Peripartum women receiving routine care or other therapies not involving physical activity intervention served as the control group. Outcome Measures: The primary outcome measures include the incidence of GDM/T2D after GDM and the results of the 75-gram oral glucose tolerance test (75g-OGTT). Study Design: Randomized controlled trials (RCTs) as the analysis type in the literature.

2.2.2 Exclusion criteria

Participants: Pregnant women with a history of diabetes or a family history of diabetes, and those with contraindications to exercise. Intervention: Studies where the intervention does not include exercise. Control: Studies lacking information on the control group. Data: Studies with incomplete data or studies from which valid data cannot be extracted. Study Types: Conference reports, protocols, case reports, reviews, and editorial materials.

2.3 Quality assessment and data extraction

According to the preliminary risk assessment guidelines recommended by the Cochrane Collaboration, the following parameters were considered in the analysis: adequate random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias (Figure 1). In the following steps, we integrated the relevant data from all the studies, mainly categorized into three groups, namely, outcome indicators of exercise therapy in the prevention, treatment, and post-prognosis stages of GDM. These indicators include GDM incidence, 75g-OGTT results, and Type 2 Diabetes (T2D) incidence. Subsequently, we conducted independent meta-analyses for these three categories of data to determine whether there are differences in the intervention effects of exercise management for GDM across these three stages.

2.4 Statistical analyses

Using RevMan 5.4 software, the mean and standard deviation of the 75g oral glucose tolerance test (75g-OGTT) in the experimental and control groups after exercise intervention, as well as the incidence data of gestational diabetes mellitus (GDM) and type 2 diabetes after GDM, were analyzed. The 75g-OGTT is a clinical laboratory examination used to assess an individual's blood sugar metabolism. This test involves the oral consumption of a 75-gram glucose solution while the individual is in a fasting state. Subsequently, blood glucose levels are measured at different time intervals, typically including 0 hours (fasting), 1 hour, and 2 hours after glucose ingestion.

The above content falls into the category of continuous data, and we calculated the effect size (MD) and its 95% confidence interval for the experimental and control groups in each study. By summarizing the results from all randomized controlled trials (RCTs) included in the meta-analysis, we could determine whether there was an improvement in fasting blood glucose and blood glucose 2 hours after ingestion. This depended on whether there was a significant difference in the outcomes between the experimental and control groups. If MD was positive, it indicated that the mean of the experimental group was higher than that of the control group, and if MD was negative, it indicated that the control group's mean was higher than that of the experimental group.

Regarding the incidence rates of GDM and type 2 diabetes after GDM, the data are dichotomous. We used Relative Risk (RR) to compare the differences in the incidence rates of gestational diabetes and type 2 diabetes after GDM between the exercise group and the control group. If RR equaled 1, then the incidence rates in both groups were equal; if RR was greater than 1, it indicated a higher incidence rate in the exercise group, and if RR was less than 1, it indicated a lower incidence rate in the exercise group. Whether it was continuous or dichotomous outcomes, if I^2 was less than or

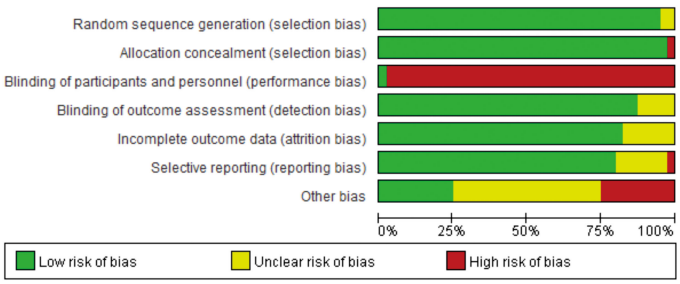

FIGURE 1
Bias risk assessment of included studies.

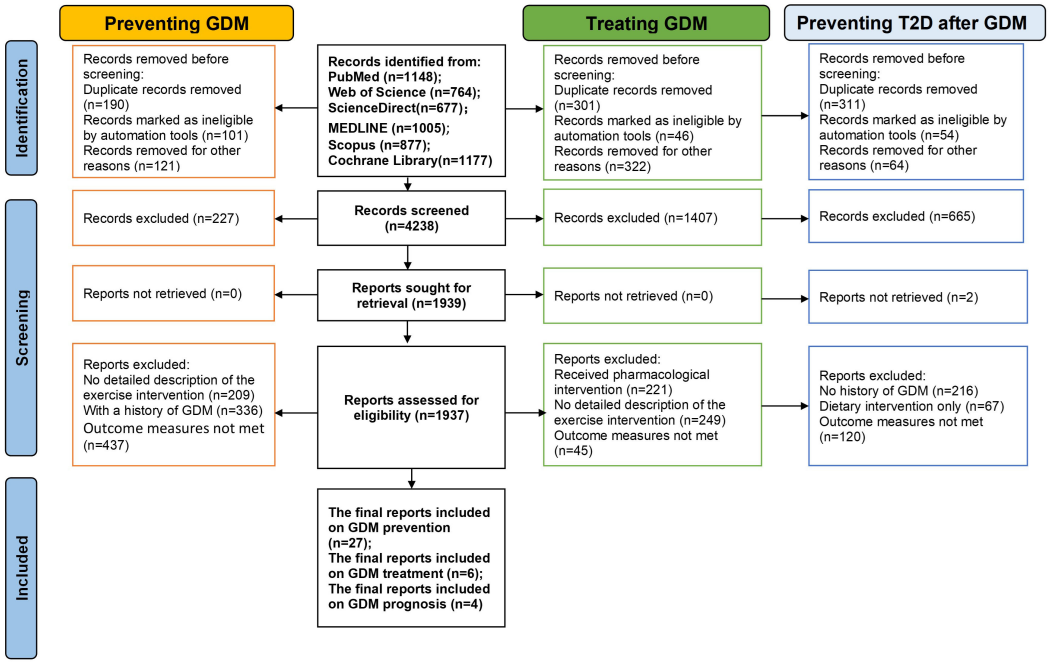

FIGURE 2
PRISMA flow diagram of study selection.

equal to 50%, it indicated low heterogeneity. Conversely, if I^2 was greater than 50%, it indicated high heterogeneity.

3 Results

3.1 Search results

The final inclusion comprises 37 studies (Figure 2), with a cumulative sample size of 10,699 participants, the publication years ranged from 1999 to 2022. Among them, there are 27 reports specifically focusing on the relationship between exercise and the prevention of Gestational Diabetes Mellitus (GDM) (11–37), 6 reports on exercise and GDM treatment (38–43), and 4 reports on exercise and the prevention of T2D following GDM (44–47). Of course, in the post-GDM prognosis stage, other chronic diseases may also emerge, but this study specifically selected the highest-risk T2D for investigation.

3.2 Characteristics of the included studies

In the end, we included basic information from 37 studies, as detailed in Table 1. The table includes sample information for both the experimental and control groups, covering the country or region of the sample, sample size, lost samples, subjects' age, body mass index (BMI), exercise intervention duration, exercise attendance rate, perceived exercise intensity, and outcome indicators. The exercise intervention plans and implementation details for the experimental group can be found in Table 1, which includes comprehensive exercise prescriptions for all studies. By summarizing and integrating the exercise interventions for GDM and subsequent T2D, along with their basic information, we arrived at the following conclusions. Firstly, compared to the post-GDM stage, exercise prescriptions for T2D prevention in the pre-GDM and treatment stages are more precise and detailed. Ninety percent of the studies provided detailed descriptions of the frequency, intensity, time, type, volume, and progression monitoring (FITT-VP) principles, offering a comprehensive implementation process for the exercise prescription (Supplementary File 2). Secondly, the exercise intervention period in the pre-GDM and treatment stages is relatively short, typically ranging from 6 to 30 weeks of intervention during pregnancy, whereas the exercise intervention time in the post-GDM stage is usually over one year (Table 1). Thirdly, the average exercise adherence is higher in the pre-GDM and treatment stages (≥80%), while in contrast, exercise adherence in the post-GDM stage is generally lower (<50%) (Table 1). These factors may contribute to significant differences in intervention effects across different stages of GDM management. We first integrated relevant data from all studies and then used the results of meta-analyses to determine whether there were significant differences in the intervention effects of exercise management for GDM across these three stages.

3.3 Quality assessment of included studies

According to the preliminary risk assessment for publication bias as recommended by the Cochrane Collaboration. The overall

TABLE 1 Information of included studies.

Author (Year)	Country	Management stages of GDM	Sample size (E/C)	Lost to follow-up (E/C)	Age	Baseline BMI	Intervention duration (week of pregnancy)	Borg's scale	Exercise adherence	Outcome
Antoun 2020 (11)	England	GDM prevention	294/263	0/0	≥16	≥30	8th~39th	NA	NA	GDM incidence
Barakat 2012 (12)	Spain	GDM prevention	40/43	0/0	32 ± 4	22.7 ± 2.8	6th~39th	NA	high	GDM incidence
Barakat 2013 (13)	Spain	GDM prevention	225/225	15/7	31 ± 3	24.1 ± 4.1	10th~39th	10~12	high	GDM incidence
Barakat 2014 (14)	Spain	GDM prevention	107/93	0/3	31.54 ± 3.86	23.78 ± 4.4	9th~40th	12~13	NA	GDM incidence
Barakat 2019 (8)	Spain	GDM prevention	260/260	26/38	31.75 ± 4.68	23.50 ± 3.79	8th~39th	12~14	high	GDM incidence
Bisson 2015 (16)	Canadian	GDM prevention	25/25	1/1	30.5 ± 3.7	35.2 ± 5.4	15th~27th	NA	moderate	GDM incidence
Callaway 2010 (17)	Australia	GDM prevention	25/25	3/6	NA	NA	12th~36th	NA	moderate	GDM incidence
Cordero 2015 (18)	Spain	GDM prevention	101/156	0/0	33.24 ± 4.3	22.5 ± 3.2	10 th~40th	12~14	high	GDM incidence
Ko 2014 (22)	American	GDM prevention	591/605	13/59	26.0 ± 4.8	26.0 ± 4.8	18th~36th	NA	low	GDM incidence
da Silva 2017 (19)	American	GDM prevention	213/426	8/19	27.2 ± 5.3	25.2 ± 4.1	16th~36th	12~14	NA	GDM incidence
Elden 2008 (20)	Sweden	GDM prevention	131/130	1/1	29.8 ± 4.2	NA	6 weeks	NA	high	GDM incidence
Garnæs 2016 (21)	England	GDM prevention	50/50	9/14	33.1 ± 6 5.2	34.3 ± 5.6	20th~37th	NA	NA	GDM incidence
Kong 2014 (23)	American	GDM prevention	19/23	1/4	28.6 ± 5.3	34.7 ± 4.6	12th~35 h	NA	NA	GDM incidence
Nobles 2015 (24)	American	GDM prevention	143/147	19/20	16~40	25~40	12 weeks	NA	high	GDM incidence
Okido 2015 (25)	Brazil	GDM prevention	48/48	22/14	23.41 ± 5.31	24.12 ± 4.31	20th~36th	NA	NA	GDM incidence
Oostdam 2012(26)	Netherlands	GDM prevention	62/59	13/7	30.8 ± 5.2	33.0 ± 3.7	24th~40th	12~14	low	GDM incidence
Pelaez 2019 (27)	Spain	GDM prevention	100/201	0/0	31.07 ± 3.19	24.1 ± 4.4	12th~36th	12~14	high	GDM incidence
Price 2012(28)	American	GDM prevention	31/31	0/0	30.5 ± 5	26.6 ± 3.1	12th~36th	12~14	high	GDM incidence
Renault 2014-PA(29)	Denmark	GDM prevention	125/134	0/0	30.9 ± 4.9	34.1 ± 4.4	13th~37th	NA	high	GDM incidence
Ruiz 2013 (30)	Spain	GDM prevention	481/481	0/0	31.6 ± 4	23.7 ± 3.9	9th~39th	10~12	high	GDM incidence

(Continued)

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TABLE 1 Continued

Author (Year)	Country	Management stages of GDM	Sample size (E/C)	Lost to follow-up (E/C)	Age	Baseline BMI	Intervention duration (week of pregnancy)	Borg's scale	Exercise adherence	Outcome
Seneviratne 2015 (31)	New Zealand	GDM prevention	38/37	1/0	18~40	≥25	20th~35th	NA	low	GDM incidence
Simmons 2015 (32)	9 European countries	GDM prevention	50/50	15/14	33.1 ± 5.2	34.5 ± 4.5	20th ~37th	NA	NA	GDM incidence
Simmons 2017 (33)	9 European countries	GDM prevention	110/105	21/11	31.7 ± 5.1	33.7 ± 4.0	24th~37th	NA	NA	GDM incidence
Tomić V 2013 (34)	Croatia	GDM prevention	166/168	0/0	28.9	23.1 ± 4.1	6th~40th	NA	NA	GDM incidence
Uria-M 2022 (35)	Spain	GDM prevention	130/130	28/29	33.80 ± 3.27	22.70 ± 4.17	8th~39th	12~14	high	GDM incidence
Ussher 2015 (36)	England	GDM prevention	392/393	2/2	27.2 ± 6.1	25.6 ± 5.0	15th~40th	NA	low	GDM incidence
Wang 2016 (37)	China	GDM prevention	150/150	18/17	32.14 ± 4.57	26.75 ± 2.74	12th~37th	12~14	high	GDM incidence
Zhao 2022 (43)	China	GDM treatment	64/60	0/0	31.2 ± 4.1	NA	13 weeks	13~14	moderate	75g-OGTT
Jin 2022 (40)	China	GDM treatment	67/67	2/1	33.51 ± 4.27	21.31 ± 3.20	12 weeks	NA	high	75g-OGTT
Gao 2019 (38)	China	GDM treatment	49/50	6/4	31.84 ± 5.19	23.03 ± 5.22	6 weeks	13	high	75g-OGTT
Kokic 2018 (41)	Croatia	GDM treatment	20/22	2/2	32.78 ± 3.83	24.39 ± 4.89	6 weeks	NA	high	75g-OGTT
Halse 2015 (39)	Australia	GDM treatment	20/20	0/0	34 ± 5	25.2 ± 6.7	26th~37th	NA	high	75g-OGTT
Wu 2022 (42)	China	GDM treatment	75/75	NA	28.75 ± 3.93	22.00 ± 1.94	4 weeks	NA	high	75g-OGTT
Wein 1999 (47)	Melbourne	GDM prognosis	100/100	3/4	39.5	25.2	6 years	NA	low	T2D incidence
Tandon 2022 (46)	India et.al	GDM prognosis	800/801	0/0	30.9 ± 4.9	26.6 ± 4.6	12 months	NA	low	T2D incidence

(Continued)

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TABLE 1 Continued

Author (Year)	Country	Management stages of GDM	Sample size (E/C)	Lost to follow-up (E/C)	Age	Baseline BMI	Intervention duration (week of pregnancy)	Borg's scale	Exercise adherence	Outcome
Rather 2008 (45)	American	GDM prognosis	117/122	3/4	43.0 ± 7.6	34.2 ± 6.2	3 years	NA	low	T2D incidence
Cheung 2011 (44)	Sydney	GDM prognosis	22/21	4/5	37	27.8	12 months	NA	moderate	T2D incidence

The high, moderate, and low levels of adherence with exercise refer to attendance rates equal to or greater than 80%, between 50% and 80%, and less than or equal to 50%, respectively. "NA" indicates that information is not available in this context. "Borg's scale" refers to the "Borg Rating of Perceived Exertion (RPE) scale," which is commonly used to subjectively assess exercise intensity. It allows individuals to rate their perceived exertion during physical activity, helping to adjust and monitor the intensity level of the exercise (6: No exertion, 7-8: Extremely light; 9-10: Very light, 11-12: Light, 13-14: Somewhat hard, 15-16: Hard, 17-18: Very hard, 19-20: Maximal exertion).

risk of bias in the 37 included studies were judged to have a low risk of bias (Figure 1). Among them, the highest risk is "blinding of participants and personnel" because it is challenging to adhere to this measure in exercise therapy (48).

3.4 Publication bias analysis

The symmetrical shape of the funnel plot displayed in Figure 3 suggested that the risk of publication bias was low. Due to the limited inclusion of studies in Figures 3B–D (n < 10), the results primarily rely on observations from Figure 3A.

3.5 Outcomes of meta-analysis

3.5.1 The overall effect of exercise prescription intervention for GDM prevention

As shown in Figure 4, in this meta-analysis focused on exercise prescription for the prevention of GDM, we included 27 randomized controlled trials (RCTs) (11–37) that compared the incidence of GDM between the control group and the exercise group. The results indicate that the exercise group had a lower GDM incidence compared to the control group (p<0.00001), with a relative risk (RR) of 0.63 and a 95% confidence interval (95%CI) ranging from 0.54 to 0.72, suggesting a significant reduction in GDM incidence in the exercise group. Furthermore, the heterogeneity statistic I^2 was 41%, which is less than 50%, indicating relatively minor variability among the included studies.

3.5.2 The therapeutic effect of exercise prescription intervention on GDM

We incorporated data from 6 six RCTs (38–43). Figure 5 depict the influence of exercise therapy on fasting blood glucose and blood glucose levels two hours after a 75g-OGTT in the exercise group compared to the control group. Figure 5A illustrates the fasting blood glucose results for both groups after the intervention, with a mean difference (MD) of -0.10 and a 95% CI of (-0.16, -0.04), along with an I^2 statistic of 58%. Figure 5B depicts the results of blood glucose levels two hours after a 75g-OGTT for both groups post-intervention, with an MD of -0.27 and a 95% CI of (-0.36, -0.19), and an I^2 of 85%. In both cases, the 95% confidence intervals do not include zero, indicating that these differences in effect are statistically significant. The overall results from both forest plots are skewed in favor of the exercise group, suggesting that exercise therapy is more effective in controlling blood glucose levels compared to the control group. The I^2 values of 58% and 85% for the meta-analysis results of fasting blood glucose and blood glucose levels two hours after the test respectively indicate a moderate and high level of heterogeneity.

3.5.3 The effectiveness of exercise in preventing the development of T2D after GDM diagnosis.

Lifestyle intervention, encompassing dietary control and physical exercise, stands as a primary method for treating T2D.

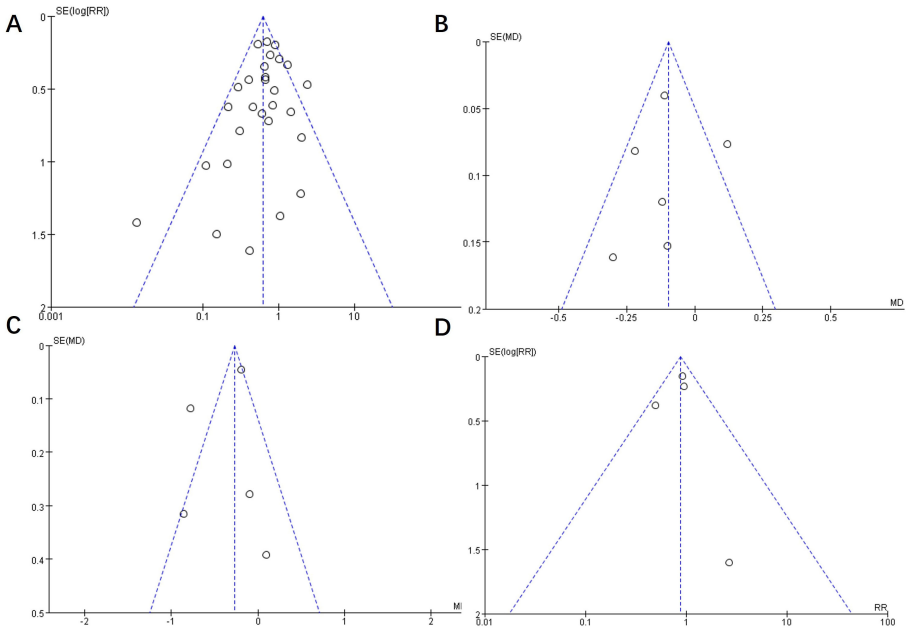

FIGURE 3
Funnel plot of publication bias of included studies. **(A)** displays a funnel plot of incidence data for exercise therapy in the prevention of GDM, while **(B, C)** respectively present funnel plots of fasting blood glucose and blood glucose two hours after a 75g -OGTT in the treatment of GDM. **(D)** shows a funnel plot of incidence data for exercise therapy in the prevention of progression from GDM to T2D.

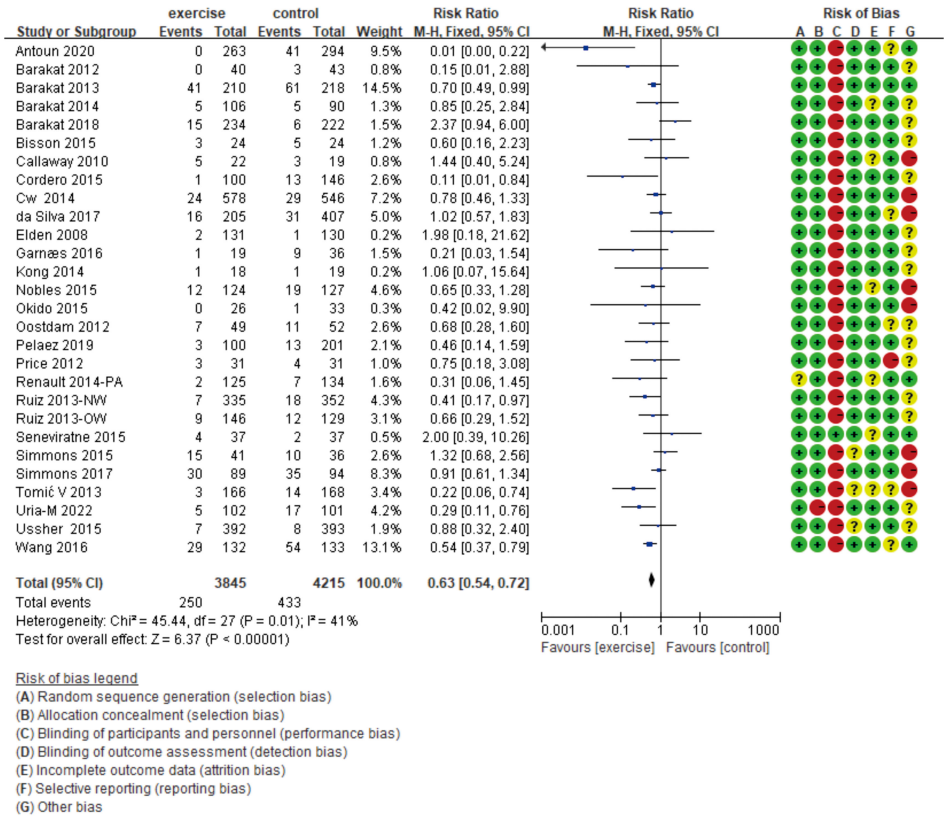

FIGURE 4
The forest plot illustrating the overall effect of exercise prescription intervention for GDM prevention.

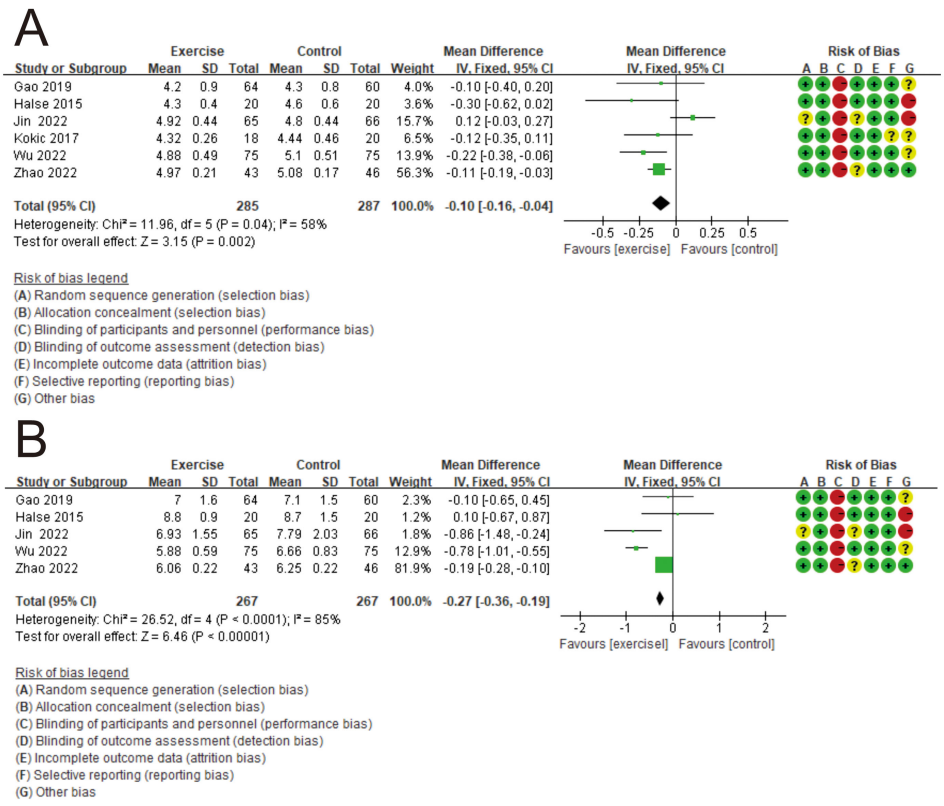

FIGURE 5
This forest plot illustrates the beneficial effects of exercise prescription intervention on 75g-OGTT. **(A)** The forest plot illustrating the control effect of exercise prescription intervention on fasting blood glucose levels. **(B)** The forest plot illustrating the control effect of exercise prescription intervention on 2-h postprandial blood glucose levels.

For women with a history of GDM, there exists the potential for T2D development postpartum. However, the need for extended follow-up introduces the challenge of potential sample loss. We identified four RCTs (44–47) that provided data on T2D incidence rates in both lifestyle intervention and control groups. As indicated in Figure 6, the results reveal a Relative Risk (RR) of 0.88, a 95% CI spanning from 0.69 to 1.11, and an I^2 statistic of 0%. These findings suggest that in these studies, lifestyle intervention did not significantly affect the risk of women with a history of GDM developing T2D.

4 Discussion

After a comprehensive study of the meta-analysis of exercise therapy in the prevention, treatment, and prognosis of GDM, this study concludes that exercise therapy shows significant intervention

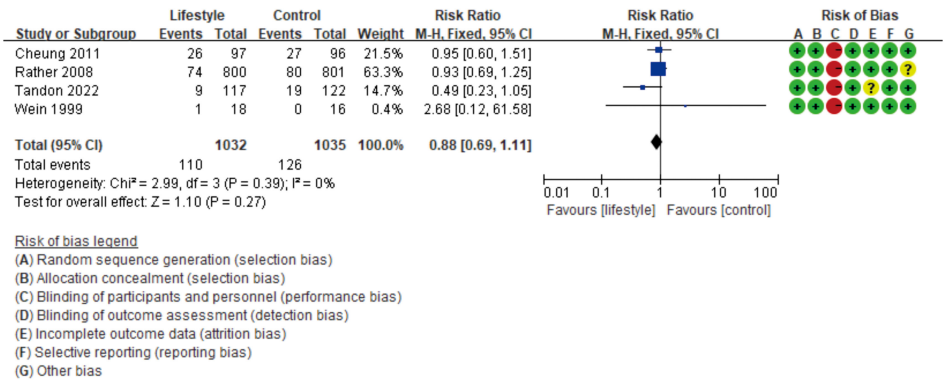

FIGURE 6
The forest plot illustrating the effectiveness of lifestyle intervention in preventing type 2 diabetes after GDM.

effects in preventing and treating GDM (Figures 4, 5), while its effectiveness in preventing T2D after GDM is not significant (Figure 6). We conducted in-depth analyses for these two distinct outcomes and proposed recommendations for exercise therapy in GDM management.

In GDM prevention and treatment studies, the "FITT-VP" framework was utilized for quantitative control (Supplementary File 2), ensuring the safety of exercise during pregnancy and experimental attendance rates. However, in studies focusing on preventing T2D after GDM, lifestyle interventions typically provided only verbal advice, lacking quantitative exercise prescriptions. According to Choi et al.'s research (2013) (49), quantitative exercise prescriptions can enhance patients' adherence to exercise. Therefore, a focus on quantitative exercise regimens is crucial in lifestyle interventions during the post-GDM period.

As women transition into the postpartum period, home-based exercise becomes part of their daily routine, and face-to-face supervision frequency decreases as their contact with the healthcare system diminishes (Supplementary File 2). This makes the implementation of postpartum exercise regimens more complex. Even with established quantitative exercise plans, women with a history of GDM still demonstrate lower actual adherence to exercise in preventing T2D postpartum (Supplementary File 2). Additionally, challenges related to exercise adherence, long-term supervision, GDM post-treatment education, and follow-up contribute to the difficulty of sustaining postpartum exercise. Therefore, overcoming challenges related to exercise adherence, long-term supervision, GDM post-treatment education, and follow-up is crucial to enhancing the intervention effects of exercise therapy in preventing T2D after GDM.

Considering the challenges in implementing exercise therapy postpartum, studies indicate that pregnancy is a critical period for preventing type 2 diabetes since women have frequent contact with the healthcare system during this time, allowing for the shaping of postpartum lifestyle choices (50, 51). Thus, this study suggests integrating the prevention of T2D in post-GDM patients with the prevention and treatment of GDM during pregnancy through exercise therapy. The aim is to leverage the favorable conditions of frequent contact between pregnant women and the healthcare system to help women acquire exercise skills, establish awareness of independent exercise, and lay the foundation for autonomous exercise postpartum.

Specifically, as shown in Figure 7, the management model includes several key aspects:

1 Pregnancy Exercise Intervention (GDM Prevention and Treatment Phases):

- Encourage healthcare professionals to develop personalized exercise prescriptions for each GDM patient, considering factors such as the patient's health condition, exercise history, time constraints, and provide clear recommendations for exercise frequency, intensity, duration, and type.
- Provide face-to-face professional supervision, including obstetricians, fitness coaches, etc., to enhance pregnant women's adherence to exercise. Professional supervision is crucial in helping pregnant women develop their awareness and methods of autonomous exercise and educating them about post-GDM sequelae.

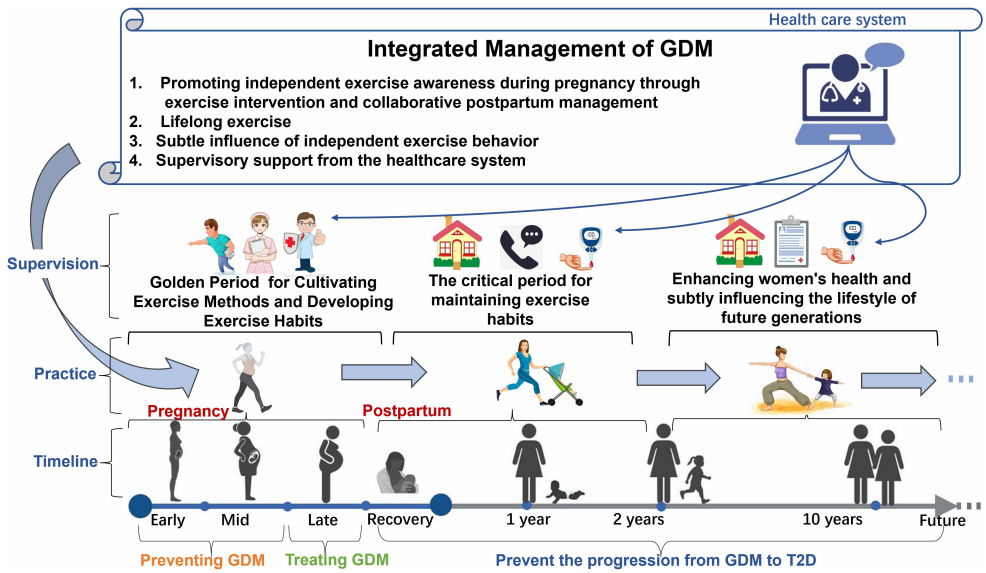

FIGURE 7
Comprehensive management model of exercise therapy for GDM.

2 Postpartum Exercise Intervention (Post-GDM Prognosis Phase):

- Within the first 1-2 years postpartum (52, 53): The personalized exercise prescriptions from the pregnancy period remain applicable, and women continue to maintain good exercise habits based on the exercise methods during pregnancy.
- Beyond 2 years (54): Employ innovative, flexible exercise plans tailored to individual needs and interests, such as diverse parent-child exercise programs.
- Emphasize personalized, long-term support using self-management education techniques, such as cognitive-behavioral techniques and motivational conversations, to help patients establish and maintain healthy exercise habits.

3 Lifelong Exercise and Implicit Autonomous Exercise Behavior:

- Continuously advocate and support women to maintain lifelong exercise, ensuring their active participation in physical activities through detailed exercise guidelines and ongoing training.
- Foster a positive family atmosphere, inspiring the next generation's autonomous exercise behavior through leading by example. This creates a healthy habit of physical activity in the family, laying a solid foundation for the children's health.

4 Supervisory Support from the Healthcare System:

- In the prevention and treatment stages of GDM, provide face-to-face supervision by a professional team as much as possible.
- In the post-GDM phase, create a support network where patients and healthcare professionals can share experiences, solve problems, and motivate each other. This can be achieved through online social platforms, regular meetings, etc. Additionally, strengthen telephone follow-ups within the first 1-2 years postpartum and encourage women to monitor blood glucose levels.

Through this integrated exercise therapy management model, the goal is to instill good exercise habits during pregnancy, perpetuate and consolidate these habits postpartum, ultimately forming a healthy pattern of lifelong exercise. By collaborating with patients and the healthcare system, providing comprehensive support and training, more significant effects can be achieved. In long-term health management, exercise not only improves the health of mothers but also has a subtle influence on shaping the next generation's good habits of autonomous exercise. Such a family exercise atmosphere contributes to promoting health throughout the entire life cycle, conveying the importance of physical activity within the family and establishing a solid foundation for the health of the children.

4.1 Limitations

There are limited studies meeting the inclusion criteria (T2D incidence rates) on the effectiveness of exercise therapy in preventing T2D after GDM, which may introduce bias. Future research should focus on long-term follow-up to expand data on T2D incidence rates. Additionally, while our meta-analysis focused on the metabolic improvements from exercise therapy in women with GDM, it did not assess its effects on cardiac function, particularly echocardiographic parameters like myocardial strain. Since GDM women may experience subclinical myocardial dysfunction (55, 56). Therefore, exercise therapy may have potential beneficial effects on the myocardial strain parameters in these women. Future research should further explore this topic to assess the role of exercise therapy in preventing and treating GDM-related cardiac complications. This will provide more comprehensive evidence for the management of GDM.

5 Conclusions

This study highlights that while exercise therapy has short-term benefits in preventing and treating GDM, its effectiveness in preventing T2D post-GDM is limited by prolonged interventions and challenges in long-term follow-up. To address metabolic concerns and instill positive exercise habits in future generations, the manuscript proposes an integrated approach for comprehensive GDM management, aimed at promoting lifelong health. Additionally, as women with GDM may have subclinical myocardial dysfunction, further research should explore exercise therapy's role in preventing GDM-related cardiac complications. Larger-scale, long-term studies are needed to confirm its effectiveness in preventing T2D and cardiac issues post-GDM, ensuring a more comprehensive management strategy.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Author contributions

HX: Conceptualization, Data curation, Methodology, Writing – original draft. RL: Conceptualization, Data curation, Funding acquisition, Methodology, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in theabsence of any commercial or financial relationships that could beconstrued as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2024.1347754/full#supplementary-material

ADDITIONAL FILE 1
Search Strategy.

ADDITIONAL FILE 2
The exercise prescription and implementation strategies.

ADDITIONAL FILE 3
Outcome measurement.

ADDITIONAL FILE 4
Risk of Bias.

ADDITIONAL FILE 5
Abbreviations.

ADDITIONAL FILE 6
Review Protocol.

PRESENTATION 1
PRISMA Checklist.

References

1. Wang H, Li N, Chivese T, Werfalli M, Sun H, Yuen L, et al. IDF diabetes atlas: estimation of global and regional gestational diabetes mellitus prevalence for 2021 by international association of diabetes in pregnancy study group's criteria. *Diabetes Res Clin Practice*. (2022) 183:109050. doi: 10.1016/j.diabres.2021.109050

2. Moses RG. The recurrence rate of gestational diabetes in subsequent pregnancies. *Diabetes Care*. (1996) 19:1348–50. doi: 10.2337/diacare.19.12.1348

3. Chiefari E, Arcidiacono B, Foti D, Brunetti A. Gestational diabetes mellitus: an updated overview. *J Endocrinological Invest*. (2017) 40:899–909. doi: 10.1007/s40618-016-0607-5

4. Vounzoulaki E, Khunti K, Abner SC, Tan BK, Davies MJ, Gillies CL. Progression to type 2 diabetes in women with a known history of gestational diabetes: systematic review and meta-analysis. *Bmj*. (2020) 369:m1361. doi: 10.1136/bmj.m1361

5. Diabetes Prevention Program Research G. 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. *Lancet*. (2009) 374:1677–86. doi: 10.1016/S0140-6736(09)61457-4

6. Davenport MH, Kathol AJ, Mottola MF, Skow RJ, Meah VL, Poitras VJ, et al. Prenatal exercise is not associated with fetal mortality: a systematic review and meta-analysis. *Br J Sports Med*. (2019) 53:108–15. doi: 10.1136/bjsports-2018-099773

7. Smith BJ, Cheung NW, Bauman AE, Zehle K, McLean M. Postpartum physical activity and related psychosocial factors among women with recent gestational diabetes mellitus. *Diabetes Care*. (2005) 28:2650–4. doi: 10.2337/diacare.28.11.2650

8. Buelo AK, Kirk A, Lindsay RS, Jepson RG. Exploring the effectiveness of physical activity interventions in women with previous gestational diabetes: A systematic review of quantitative and qualitative studies. *Prev Med Rep*. (2019) 14:100877. doi: 10.1016/j.pmedr.2019.100877

9. Page M, McKenzie J, Bossuyt P, Boutron I, Hoffmann T, Mulrow C, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ (Clinical Res ed)*. (2021) 372:n71. doi: 10.1136/bmj.n71

10. Cumpston MS, McKenzie JE, Welch VA, Brennan SE. Strengthening systematic reviews in public health: guidance in the Cochrane Handbook for Systematic Reviews of Interventions, 2nd edition. *J Public Health (Oxf)*. (2022) 44:e588–92. doi: 10.1093/pubmed/fdac036

11. Antoun E, Kitaba NT, Titcombe P, Dalrymple KV, Garratt ES, Barton SJ, et al. Maternal dysglycaemia, changes in the infant's epigenome modified with a diet and physical activity intervention in pregnancy: Secondary analysis of a randomised control trial. *PloS Med*. (2020) 17:e1003229. doi: 10.1371/journal.pmed.1003229

12. Barakat R, Cordero Y, Coteron J, Luaces M, Montejo R. Exercise during pregnancy improves maternal glucose screen at 24-28 weeks: a randomised controlled trial. *Br J Sports Med*. (2012) 46:656–61. doi: 10.1136/bjsports-2011-090009

13. Barakat R, Pelaez M, Lopez C, Lucia A, Ruiz JR. Exercise during pregnancy and gestational diabetes-related adverse effects: a randomised controlled trial. *Br J Sports Med*. (2013) 47:630–6. doi: 10.1136/bjsports-2012-091788

14. Barakat R, Perales M, Bacchi M, Coteron J, Refoyo I. A program of exercise throughout pregnancy. Is it safe to mother and newborn? *Am J Health Promotion*. (2014) 29:2–8. doi: 10.4278/ajhp.130131-QUAN-56

15. Barakat R, Refoyo I, Coteron J, Franco E. Exercise during pregnancy has a preventative effect on excessive maternal weight gain and gestational diabetes. *A randomized Controlled trial Braz J Phys Ther*. (2019) 23:148–55. doi: 10.1016/j.bjpt.2018.11.005

16. Bisson M, Alméras N, Dufresne S, Robitaille J, Rhéaume C, Bujold E, et al. A 12-week exercise program for pregnant women with obesity to improve physical activity levels: an open randomised preliminary study. *PloS One*. (2015) 10:e0137742. doi: 10.1371/journal.pone.0137742

17. Callaway LK, Colditz PB, Byrne NM, Lingwood BE, Rowlands IJ, Foxcroft K, et al. Prevention of Gestational Diabetes Feasibility issues for an exercise intervention in obese pregnant women. *Diabetes Care*. (2010) 33:1457–9. doi: 10.2337/dc09-2336

18. Cordero Y, Mottola MF, Vargas J, Blanco M, Barakat R. Exercise is associated with a reduction in gestational diabetes mellitus. *Med Sci Sports Exercise*. (2015) 47:1328–33. doi: 10.1249/mss.0000000000000547

19. da Silva SG, Hallal PC, Domingues MR, Bertoldi AD, da Silveira MF, Bassani D, et al. A randomized controlled trial of exercise during pregnancy on maternal and neonatal outcomes: results from the PAMELA study. *Int J Behav Nutr Phys Activity*. (2017) 14:1–11. doi: 10.1186/s12966-017-0632-6

20. Elden H, Ostgaard H, Fagevik-Olsen M, Ladfors L, Hagberg H. Treatments of pelvic girdle pain in pregnant women: adverse effects of standard treatment, acupuncture and stabilising exercises on the pregnancy, mother, delivery and the fetus/neonate. *BMC complementary Altern Med*. (2008) 8:34. doi: 10.1186/1472-6882-8-34

21. Garnæs K, Mørkved S, Salvesen Ø, Moholdt T. Exercise training and weight gain in obese pregnant women: A randomized controlled trial (ETIP trial). *PloS Med*. (2016) 13:e1002079. doi: 10.1371/journal.pmed.1002079

22. Ko C, Napolitano P, Lee S, Schulte S, Ciol M, Beresford S. Physical activity, maternal metabolic measures, and the incidence of gallbladder sludge or stones during pregnancy: a randomized trial. *Am J perinatology*. (2014) 31:39–48. doi: 10.1055/s-0033-1334455

23. Kong K, Campbell C, Foster R, Peterson A, Lanningham-Foster L. A pilot walking program promotes moderate-intensity physical activity during pregnancy. *Med Sci sports exercise*. (2014) 46:462–71. doi: 10.1249/mss.0000000000000141

24. Nobles C, Marcus BH, Stanek EJ, Braun B, Whitcomb BW, Solomon CG, et al. Effect of an exercise intervention on gestational diabetes mellitus A randomized controlled trial. *Obstetrics Gynecology*. (2015) 125:1195–204. doi: 10.1097/aog.0000000000000738

25. Okido M, Valeri F, Martins W, Ferreira C, Duarte G, Cavalli R. Assessment of foetal wellbeing in pregnant women subjected to pelvic floor muscle training: a controlled randomised study. *Int urogynecology J*. (2015) 26:1475–81. doi: 10.1007/s00192-015-2719-4

26. Oostdam N, van Poppel MNM, Wouters M, Eekhoff EMW, Bekedam DJ, Kuchenbecker WKH, et al. No effect of the FitFor2 exercise programme on blood glucose, insulin sensitivity, and birthweight in pregnant women who were overweight and at risk for gestational diabetes: results of a randomised controlled trial. *Bjog-an Int J Obstetrics Gynaecology*. (2012) 119:1098–107. doi: 10.1111/j.1471-0528.2012.03366.x

27. Pelaez M, Gonzalez-Cerron S, Montejo R, Barakat R. Protective effect of exercise in pregnant women including those who exceed weight gain recommendations: A randomized controlled trial. *Mayo Clinic Proc*. (2019) 94:1951–9. doi: 10.1016/j.mayocp.2019.01.050

28. Price B, Amini S, Kappeler K. Exercise in pregnancy: effect on fitness and obstetric outcomes-a randomized trial. *Med Sci sports exercise*. (2012) 44:2263–9. doi: 10.1249/MSS.0b013e318267ad67

29. Renault K, Nørgaard K, Nilas L, Carlsen E, Cortes D, Pryds O, et al. The Treatment of Obese Pregnant Women (TOP) study: a randomized controlled trial of the effect of physical activity intervention assessed by pedometer with or without dietary intervention in obese pregnant women. *Am J obstetrics gynecology*. (2014) 210:134.e1–9. doi: 10.1016/j.ajog.2013.09.029

30. Ruiz JR, Perales M, Pelaez M, Lopez C, Lucia A, Barakat R. Supervised exercise-based intervention to prevent excessive gestational weight gain: A randomized controlled trial. *Mayo Clinic Proc*. (2013) 88:1388–97. doi: 10.1016/j.mayocp.2013.07.020

31. Seneviratne SN, Derraik JGB, Jiang YN, McCowan LME, Gusso S, Cutfield WS, et al. The sex of the foetus affects maternal blood glucose concentrations in overweight and obese pregnant women. *J Obstetrics Gynaecology*. (2017) 37:667–9. doi: 10.1080/01443615.2016.1256970

32. Simmons D. Prevention of gestational diabetes mellitus: Where are we now? *Diabetes Obes Metab*. (2015) 17:824–34. doi: 10.1111/dom.12495

33. Simmons D, Devlieger R, van Assche A, Jans G, Galjaard S, Corcoy R, et al. Effect of physical activity and/or healthy eating on GDM risk: the DALI lifestyle study. *J Clin Endocrinol Metab*. (2017) 102:903–13. doi: 10.1210/jc.2016-3455

34. Tomić V, Sporiš G, Tomić J, Milanović Z, Zigmundovac-Klaić D, Pantelić S. The effect of maternal exercise during pregnancy on abnormal fetal growth. *Croatian Med J*. (2013) 54:362–8. doi: 10.3325/cmj.2013.54.362

35. Uria-Minguito A, Silva-Jose C, Sanchez-Polan M, Diaz-Blanco A, Garcia-Benasach F, Martinez VC, et al. The effect of online supervised exercise throughout pregnancy on the prevention of gestational diabetes in healthy pregnant women during covid-19 pandemic: a randomized clinical trial. *Int J Environ Res Public Health*. (2022) 19:14104. doi: 10.3390/ijerph192114104

36. Ussher M, Lewis S, Aveyard P, Manyonda I, West R, Lewis B, et al. The London Exercise And Pregnant smokers (LEAP) trial: a randomised controlled trial of physical activity for smoking cessation in pregnancy with an economic evaluation. *Health Technol Assess (Winchester England)*. (2015) 19:vii–xxiv, 1-135. doi: 10.3310/hta19840

37. Wang C, Wei YM, Zhang XM, Zhang Y, Xu QQ, Su SP, et al. Effect of regular exercise commenced in early pregnancy on the incidence of gestational diabetes mellitus in overweight and obese pregnant women: A randomized controlled trial. *Diabetes Care*. (2016) 39:E163–4. doi: 10.2337/dc16-1320

38. Guo H, Zhang Y, Li P, Zhou P, Chen L, Li S. Evaluating the effects of mobile health intervention on weight management, glycemic control and pregnancy outcomes in patients with gestational diabetes mellitus. *J endocrinological Invest*. (2019) 42:709–14. doi: 10.1007/s40618-018-0975-0

39. Halse RE, Wallman KE, Dimmock JA, Newnham JP, Guelfi KJ. Home-based exercise improves fitness and exercise attitude and intention in women with GDM. *Med Sci Sports Exerc*. (2015) 47:1698–704. doi: 10.1249/mss.0000000000000587

40. Jin Y, Chen ZF, Li JQ, Zhang W, Feng SW. Effects of the original Gymnastics for Pregnant Women program on glycaemic control and delivery outcomes in women with gestational diabetes mellitus: A randomized controlled trial. *Int J Nurs Stud*. (2022) 132:104271. doi: 10.1016/j.ijnurstu.2022.104271

41. Kokic IS, Ivanisevic M, Biolo G, Simunic B, Kokic T, Pisot R. Combination of a structured aerobic and resistance exercise improves glycaemic control in pregnant women diagnosed with gestational diabetes mellitus. *A randomised Controlled trial Women Birth*. (2018) 31:E232–8. doi: 10.1016/j.wombi.2017.10.004

42. Wu Y, Xu M, Zheng G. Application of diversified and quantitative management model of exercise intervention in patients with gestational diabetes mellitus. *J Matern Fetal Neonatal Med*. (2022) 35:5001–7. doi: 10.1080/14767058.2021.1874340

43. Zhao HF, Xie YP, Zhao MJ, Huang HB, Liu CH, Huang FF, et al. Effects of moderate-intensity resistance exercise on blood glucose and pregnancy outcome in patients with gestational diabetes mellitus: A randomized controlled trial. *J Diabetes Its Complications*. (2022) 36:108186. doi: 10.1016/j.jdiacomp.2022.108186

44. Cheung NW, Smith BJ, van der Ploeg HP, Cinnadaio N, Bauman A. A pilot structured behavioural intervention trial to increase physical activity among women with recent gestational diabetes. *Diabetes Res Clin Practice*. (2011) 92:E27–9. doi: 10.1016/j.diabres.2011.01.013

45. Ratner R, Christophi C, Metzger B, Dabelea D, Bennett P, Pi-Sunyer X, et al. Prevention of diabetes in women with a history of gestational diabetes: effects of metformin and lifestyle interventions. *J Clin Endocrinol Metab*. (2008) 93:4774–9. doi: 10.1210/jc.2008-0772

46. Tandon N, Gupta Y, Kapoor D, Lakshmi JK, Praveen D, Bhattacharya A, et al. Effects of a lifestyle intervention to prevent deterioration in glycemic status among south asian women with recent gestational diabetes A randomized clinical trial. *JAMA Network Open*. (2022) 5:e220773. doi: 10.1001/jamanetworkopen.2022.0773

47. Wein P, Beischer N, Harris C, Permezel M. A trial of simple versus intensified dietary modification for prevention of progression to diabetes mellitus in women with impaired glucose tolerance. *Aust New Z J Obstetrics Gynaecology*. (1999) 39:162–6. doi: 10.1111/j.1479-828X.1999.tb03363.x

48. Smart NA, Waldron M, Ismail H, Giallauria F, Vigorito C, Cornelissen V, et al. Validation of a new tool for the assessment of study quality and reporting in exercise training studies: TESTEX. *Int J Evid Based Healthc*. (2015) 13:9–18. doi: 10.1097/xeb.0000000000000020

49. Choi J, Fukuoka Y, Lee JH. The effects of physical activity and physical activity plus diet interventions on body weight in overweight or obese women who are pregnant or in postpartum: a systematic review and meta-analysis of randomized controlled trials. *Prev Med*. (2013) 56:351–64. doi: 10.1016/j.ypmed.2013.02.021

50. Adam S, McIntyre HD, Tsoi KY, Kapur A, Ma RC, Dias S, et al. Pregnancy as an opportunity to prevent type 2 diabetes mellitus: FIGO Best Practice Advice. *Int J Gynecology Obstetrics*. (2023) 160:56–67. doi: 10.1002/ijgo.v160.S1

51. Phelan S. Pregnancy: a "teachable moment" for weight control and obesity prevention. *Am J Obstetrics Gynecology*. (2010) 202:135.e1–8. doi: 10.1016/j.ajog.2009.06.008

52. McIntyre HD, Peacock A, Miller YD, Koh D, Marshall AL. Pilot study of an individualised early postpartum intervention to increase physical activity in women with previous gestational diabetes. *Int J Endocrinol*. (2012) 2012:892019. doi: 10.1155/2012/892019

53. Metzger BE, Bybee DE, Freinkel N, Phelps RL, Radvany RM, Vaisrub N. Gestational diabetes mellitus. Correlations between the phenotypic and genotypic characteristics of the mother and abnormal glucose tolerance during the first year postpartum. *Diabetes*. (1985) 34 Suppl 2:111–5. doi: 10.2337/diab.34.2.s111

54. O'Sullivan JB. Establishing criteria for gestational diabetes. *Diabetes Care*. (1980) 3:437–9. doi: 10.2337/diacare.3.3.437

55. Li W, Li Z, Liu W, Zhao P, Che G, Wang X, et al. Two-dimensional speckle tracking echocardiography in assessing the subclinical myocardial dysfunction in patients with gestational diabetes mellitus. *Cardiovasc Ultrasound*. (2022) 20:21. doi: 10.1186/s12947-022-00292-3

56. Sonaglioni A, Barlocci E, Adda G, Esposito V, Ferrulli A, Nicolosi GL, et al. The impact of short-term hyperglycemia and obesity on biventricular and biatrial myocardial function assessed by speckle tracking echocardiography in a population of women with gestational diabetes mellitus. *Nutrition Metab Cardiovasc Diseases*. (2022) 32:456–68. doi: 10.1016/j.numecd.2021.10.011

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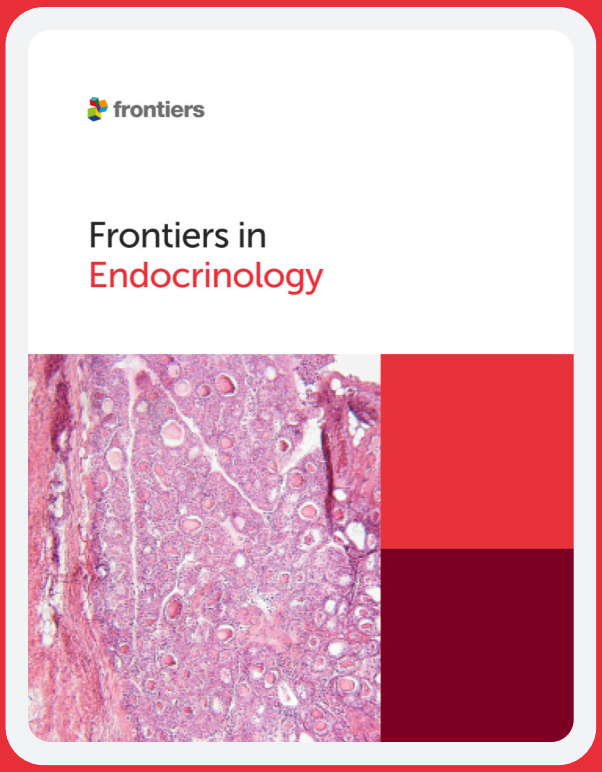

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