

Effects of High-Intensity Interval Training on Glycemic Control in Animal Models of Type 2 Diabetes Mellitus

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Abstract

Objective To explore the effect of high-intensity interval training (HIIT) on blood glucose control in experimental animals with type 2 diabetes mellitus (T2DM) and to evaluate the quality of the included studies.

Methods Literature was obtained by searching PubMed, EMBase, Web of Science, BIOSIS Preview and Cochrane Library. Chinese literature was obtained through CNKI, WanFang Data, SinoMed and VIP Database. Studies were collected and screened strictly according to inclusion/exclusion criteria. The methodological quality and reporting quality of the included studies were evaluated using SYRCLE's risk of bias tool for animal studies (SYRCLE) and Animal Research: Reporting In Vivo Experiments guidelines 2.0 (ARRIVE 2.0). Outcomes such as body weight (BW), fasting blood glucose (FBG), fasting insulin (FINS), homeostasis model assessment of insulin resistance (HOMA) were meta-analyzed and the quality of evidence was evaluated using Grading of Recommendations Assessment, Development and Evaluation (GRADE).

Results Twenty studies were included, including male mice (9) or rats (11). T2DM models were established mainly in two ways: high-fat diet and/or combined with streptozotocin (STZ) injection (15 articles), genetic modification (5 articles). Exercise and interval intensity were measured using VO₂ max, maximum speed and slope, with 1-4.5 minutes of exercise and 15 seconds-3 minutes of interval, and the training duration was 8-13 weeks with 3-5 sessions per week. The SYRCLE assessment results were mainly uncertain; none of the individual items or single studies assessed by ARRIVE 2.0 appeared complete. Standardized mean difference (SMD) combined effect size showed that compared with the sedentary control group, heterogeneity was large for all outcomes, and there were significant differences in FBG and HOMA. All evidence assessed by GRADE was of very low quality.

Conclusions The effect of HIIT on blood glucose control is clear, but the influencing factors are complex, the risk of bias is high, the reporting quality is low, the source of heterogeneity in outcomes is complex, and the quality of evidence is extremely low, which questions its reliability and validity. It is recommended to use ARRIVE 2.0 as a guide to increase the integrity and transparency of research information and improve research quality through experimental protocol registration and supplementary materials.

Full Text

Preamble

Effect of High-Intensity Interval Training on Blood Glucose Control in Experimental Animal Models of Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis

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Author Contributions: Jun Tan drafted and revised the manuscript. Lan Zheng conceptualized the research and designed the study protocol. Yan Yu, Huai Deng, Zhongrong Liu, and Qin Yi collected and analyzed the data.

Abstract

Objective: To investigate the effects of high-intensity interval training (HIIT) on blood glucose control in experimental animal models of type 2 diabetes mellitus (T2DM) and to evaluate the quality of included studies.

Methods: We systematically searched PubMed, Embase, Web of Science, BIOSIS Preview, and the Cochrane Library for English-language literature, and CNKI, WanFang Data, SinoMed, and VIP Database for Chinese literature. Study selection was conducted strictly according to predefined inclusion and exclusion criteria. Methodological quality and reporting quality were assessed using SYRCLE's risk of bias tool for animal studies and the Animal Research: Reporting of In Vivo Experiments guidelines 2.0 (ARRIVE 2.0). Outcomes including body weight (BW), fasting blood glucose (FBG), fasting insulin (FINS), and homeostasis model assessment of insulin resistance (HOMA) were meta-analyzed, and evidence quality was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.

Results: Twenty studies were included, involving male mice (9 studies) or rats (11 studies). T2DM models were developed primarily through high-fat diet feeding with or without streptozotocin (STZ) injection (15 articles) or through genetic modification (5 articles). Exercise intensity and intervals were measured using VO_2 max, maximum speed, and slope, with exercise durations of 1-4.5 minutes and intervals of 15 seconds to 3 minutes. Training lasted 8-13 weeks at a frequency of 3-5 sessions per week. SYRCLE assessment results

were predominantly uncertain, and no single study met all ARRIVE 2.0 criteria. Meta-analysis using standardized mean difference (SMD) showed significant heterogeneity across studies. Compared with sedentary controls, HIIT produced significant reductions in FBG and HOMA, though the absolute effect sizes varied considerably. GRADE assessment rated all evidence as very low quality.

Conclusions: While HIIT appears to have clear effects on blood glucose control, the evidence is compromised by complex influencing factors, high risk of bias, poor reporting quality, substantial outcome heterogeneity, and extremely low overall evidence quality, which questions the reliability and validity of findings. We recommend using ARRIVE 2.0 as a guide to improve research transparency and quality through comprehensive experimental protocol registration and detailed reporting.

Keywords: Type 2 Diabetes Mellitus; Experimental Animals; High-Intensity Interval Training; Systematic Review; Meta-Analysis

Type 2 diabetes mellitus (T2DM) is a serious metabolic disease with increasing incidence worldwide, representing an unprecedented and largely uncontrolled pandemic. Notably, one in four diabetic patients globally originates from China [1], and the prevalence among Chinese adults aged 18 and older has risen from 10.4% in 2013 to 11.2% in 2017 [2]. High-intensity interval training (HIIT) has emerged as a popular exercise concept and methodology, ranking among the top five global fitness trends for eight consecutive years as of 2021 according to the American College of Sports Medicine [3]. HIIT can improve insulin sensitivity in adults and may confer greater cardiovascular benefits for individuals at high risk of T2DM [4]. However, critical questions remain regarding the biological mechanisms of HIIT in T2DM patients, its effects on complications and other important outcomes, its advantages compared to other exercise interventions, and its safety profile. Due to the lengthy duration, difficulty, and potential risks to participants in clinical experimental research, current evidence remains very limited and conclusions are unclear [5].

Animal experiments offer a valuable alternative research strategy, and many investigators have employed animal models to address these questions. However, HIIT as an exercise intervention exerts broad, holistic effects on the organism, with slower and reversible outcomes compared to pharmacological interventions. Experimental factors are numerous and complex, and improper handling can compromise research quality and lead to erroneous conclusions. The methodological rigor and reporting quality of current animal experiments investigating HIIT interventions in T2DM, along with the characteristics of their research outcomes, are prerequisites for determining the value of these animal studies. This study employs systematic review and meta-analysis methodology to synthesize the evidence, aiming to provide researchers with high-quality evidence, optimize experimental protocols, and reduce redundant studies. Our goal is to maximize the extraction of health-promoting information from animal experimental research while upholding the principles of reduction, replacement, and refinement (3Rs) for animal experimentation.

This research protocol was registered with PROSPERO (registration code: CRD42021244120). The report was completed according to the protocol and the actual characteristics of included studies, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) statement. Both the full text and abstract were checked against the PRISMA 2020 checklist, with verification results provided in Supplementary Appendices 1 and 2.

1. Methods

1.1 Inclusion and Exclusion Criteria

Inclusion and exclusion criteria were established based on the PICOS principle (Participants, Interventions, Comparisons, Outcomes, Study design).

1.1.1 Inclusion Criteria

(1) Study design: Experimental studies; (2) Participants: T2DM animal models, with no restrictions on species; (3) Intervention and control protocols: HIIT defined as exercise intensity $>80\text{--}95\%$ VO_2max or equivalent peak heart rate (HRpeak) or equivalent running speed, with no restrictions on specific exercise type, exercise time, interval duration, training duration, or frequency. No restrictions were placed on control groups; (4) Outcomes: Body weight (BW), fasting blood glucose (FBG), fasting insulin (FINS), and homeostasis model assessment of insulin resistance (HOMA).

1.1.2 Exclusion Criteria

Duplicate publications; in vitro studies, cell and tissue culture studies, and human studies; observational studies, systematic review protocols, traditional reviews, and systematic reviews/meta-analyses; literature for which full text could not be obtained (e.g., conference abstracts); multiple publications from the same study were counted as a single study to avoid duplicate outcome inclusion.

1.2 Literature Search Strategy

We searched PubMed, Embase, Web of Science, BIOSIS Preview, Cochrane Library, CNKI, WanFang, VIP, and SinoMed databases from inception to August 23, 2021, with no restrictions on publication year or language. A supplementary search strategy was employed by reviewing reference lists of relevant systematic reviews/meta-analyses and included original studies to identify additional eligible articles. In accordance with PRISMA 2020 requirements, detailed search formulas and results for each database are provided in Appendix 3 and the supplementary document package.

1.3 Literature Screening and Data Extraction

Literature screening and data extraction were completed independently by two researchers, with a third researcher summarizing findings. Discrepancies were resolved through discussion among all three researchers.

1.3.1 Literature Screening

Retrieved literature was imported into EndNote software, where duplicates were identified using the “Find Duplicates” function combined with manual verification. Titles and abstracts were then screened to exclude studies not meeting inclusion criteria, including review articles, human studies, non-animal studies, and non-T2DM studies. Full texts were obtained for potentially eligible studies, with authors contacted by email if web-based searches lacked necessary data. Two researchers independently read full texts, applied exclusion criteria, and screened each article individually. For multiple publications from the same study, one publication was retained based on the most complete outcome data, with preference given to journal articles or more recent publications.

1.3.2 Data Extraction

Data were extracted directly from text, tables, and graphs. When data were presented only graphically, the GetData Graph Digitizer software was used for extraction. Extracted data were organized into three tables: (1) Basic information table including first author, publication year, country, animal species, ethical approval, funding support, outcomes, and comments; (2) Experimental design table including animal information and T2DM induction methods (strain, sample size, age, sex, weight, temperature, humidity, lighting, drug administration details, dose, site, frequency, success criteria, and intervention group sample size); (3) Interventions and comparison measures table including exercise type, intensity, duration, interval exercise parameters, repetition number, frequency, program duration, and control measures. All outcomes were continuous variables: BW (g), FBG (mmol/L), FINS (mmol/L), and HOMA. Authors were contacted by email (up to two attempts) for unreported or unclear data.

1.4 Quality Assessment

1.4.1 Risk of Bias Assessment

The SYRCLE (Systematic Review Centre for Laboratory Animal Experimentation) risk of bias tool for animal studies was used [6]. As detailed in Appendix 4, SYRCLE evaluates six domains: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other biases, comprising 10 items including sequence generation, baseline characteristics, allocation concealment, random housing, blinding, randomized outcome assessment, incomplete outcome reporting, selective outcome reporting, and other bias sources. Judgments of “Yes,” “No,” or “Unclear” were made and expressed as percentages.

1.4.2 Reporting Quality Evaluation

Reporting quality was assessed using the Animals in Research: Reporting In Vivo Experiments (ARRIVE) guidelines 2.0, updated by the National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs) in July 2020 [7]. The ARRIVE 2.0 Executive Questionnaire provided by NC3Rs in March 2021 (Appendix 5) was used to evaluate reporting quality based on key items, with final completeness percentages calculated and horizontal comparisons performed across questionnaire items.

1.5 Statistical Analysis and Meta-Analysis

Meta-analysis was performed using Stata 16.0 and Review Manager 5.4 software. All outcomes were expressed as mean $\pm$ standard deviation (mean $\pm$ SD). When original studies reported data as mean $\pm$ standard error (mean $\pm$ SEM), conversion was performed using the formula $SD = SEM \times \sqrt{n}$. Effect sizes were pooled using standardized mean difference (SMD) with 95% confidence intervals (95% CI). Heterogeneity was assessed using the Q test ($\alpha = 0.10$). When $I^2 \leq 50\%$, a fixed-effects model was used; when $I^2 > 50\%$, a random-effects model was employed. Sources of heterogeneity were explored through sensitivity analysis, subgroup analysis, and univariate meta-regression. Potential sources included species, modeling methods, and exercise protocols. Statistical significance was set at $P < 0.05$.

1.6 Evidence Quality Evaluation

Evidence quality for outcomes was assessed using the GRADE system [8]. Two researchers independently used the GRADEpro GDT online tool to rate evidence quality across five domains: study limitations, publication bias, imprecision, inconsistency, and indirectness [9]. Results were cross-checked, with disputes resolved by the study supervisor.

2. Results

2.1 Literature Search and Screening

The initial search yielded 446 articles (35 Chinese, 411 English), which were imported into EndNote. After eliminating 96 duplicates through author, journal, publication date, and title verification, 350 articles remained. Title and abstract screening excluded review studies, human studies, other animal models (e.g., obesity, heart failure), and conference abstracts, leaving 29 full-text articles (8 Chinese, 21 English). One Korean study was translated using WPS and Youdao translation tools. The Persian study by ESMAEILI S (2018) was interpreted using the English title, abstract, keywords, and professional Persian translation services. The detailed screening process is shown in Appendix 6.

2.2 Characteristics of Included Studies

2.2.1 Basic Information

Table 1 summarizes the 29 full-text articles reviewed. Twelve studies used mice (all C57BL strain), while 17 used rats (13 Wistar, 3 Sprague-Dawley, 1 OLETF). Eighteen studies reported ethical committee approval, and eight received funding support. Geographically, 12 studies originated from China (7 mice, 5 rats), 11 from Iran (all rats), 3 from Norway, and 1 each from France, the United States, and South Korea. All non-US studies used mice. During full-text review, studies with identical research designs and outcomes were identified as duplicates. Criteria for identifying duplicate studies included identical or par-

tially identical outcomes with identical intervention protocols. When duplicates were identified, the study with the most complete outcomes was retained, with preference for journal articles or more recent publications. ESMAEILI S (2018), Amri J (2019), and Mohammad P (2019) shared intervention protocols and some results, so Amri J (2019) with the most outcomes was retained. ZHENG L (2020) and Zheng Lifang (2021) were duplicates, with the journal publication retained. Similar duplicate handling was applied to Kalaki-Jouybari F (2020) and KHAKDAN S (2020), Xing Xiaorui (2019) and Li Xun (2018), and Zhang Q (2020) and Zhang Qiang (2017). Lin Sen (2020) and Zhang Xiaofei (2020) represented the same study using pre-diabetes induction exercise protocols, which did not meet our inclusion criteria. ROLIM N (2015) was excluded for not meeting inclusion criteria, leaving 20 studies for final inclusion.

2.2.2 Experimental Design

Table 2 presents the experimental designs of the 20 included studies, all of which were controlled group experiments. While most studies mentioned temperature, humidity, and lighting conditions, details were generally lacking. For T2DM induction, four studies used db/db mice and one used OLETF rats. KHAKDAN S (2020) employed a simple high-fat high-fructose diet (HFHFD), SABOURI M (2020) and Amri J (2019) used streptozotocin (STZ) alone, and the remaining 12 studies combined high-fat diet with STZ injection. STZ was administered intraperitoneally as a single injection in all but one study, though timing and dosage varied considerably. Zhang Q (2020) reported STZ injection followed by high-fat diet, while others administered STZ after 12 weeks of high-fat feeding. STZ was typically dissolved in fresh sodium citrate buffer at pH 4.4–4.5. Mouse studies used doses of 100 mg/kg or 10 mg/kg, while rat studies used 30–65 mg/kg. Sample sizes ranged from 6–8 animals per group. T2DM induction success was determined by FBG values using thresholds of \$ \$16.7 mmol/L, \$ \$13.8 mmol/L, or \$ \$11.1 mmol/L, though db/db mice and OLETF rats lacked explicit success criteria. The sample size for SABOURI M (2020) was unclear, and YAZDANI F (2020) showed inconsistencies between reported group sizes ($n=8/\text{group}$) and body weight data ($n=10/\text{group}$). Authors were contacted but did not respond. MOGHADDAMI K (2018) contained errors in degrees of freedom conversion and blood glucose unit conversion (mg/dL to mmol/L).

2.2.3 HIIT Intervention and Control Measures

Table 3 details the interventions. All studies used treadmill exercise for both high-intensity and interval training. Mouse high-intensity speeds ranged 15–26 m/min, while rat speeds ranged 25–36 m/min, with weekly increments of 1–2 m/min. Slopes of 15°, 20°, and 25° were used, with intensity specified as 80–95% VO_2max . Exercise duration was 2–4 minutes per bout, repeated 4–13 times. Intervals consisted of low-to-moderate intensity exercise at 0–75% VO_2max . Training frequency was 3–6 sessions per week. Control groups included sedentary, continuous exercise, and moderate-intensity intermittent exercise conditions. Training duration across studies ranged from 8–13 weeks, with 15 studies using 8 weeks, one study (Stolen 2009) using 13 weeks, and four studies using 10–12 weeks.

2.3 Quality Assessment

2.3.1 Risk of Bias

SYRCLE assessment (Figure 1) revealed that selection bias, performance bias, detection bias, attrition bias, reporting bias, and other biases could not be determined from the published reports. Only three studies could be definitively rated as low risk for selection and other biases.

2.3.2 Reporting Quality

ARRIVE 2.0 evaluation of the 20 included studies (Figure 2) assessed the 10 key items of the executive questionnaire covering study design, sample size, inclusion/exclusion criteria, randomization, blinding, outcome measures, statistical methods, experimental animals, procedures, and results. The evaluation comprised 18 questions answered as “yes” or “no.” Nearly all studies failed to report details on randomization and blinding. The rationale for sample size determination, effect size magnitude, and confidence intervals were not provided. Additionally, determination and statistical handling of the experimental unit were not reported, and whether data met statistical assumptions was overlooked. The complete reporting rate for all studies was below 80%, though reporting of experimental animal characteristics and outcomes was relatively complete.

2.4 Meta-Analysis Results

2.4.1 Meta-Analysis Findings

Table 4 presents the meta-analysis results. For comparisons between HIIT and sedentary controls, heterogeneity was substantial ($I^2 > 50\%$, $P < 0.1$) for all outcomes except BW and HOMA when compared to exercise controls, which showed no significant heterogeneity ($I^2 < 50\%$, $P > 0.1$) and thus used fixed-effects models. Random-effects models were used for all other outcomes. Compared with sedentary controls, HIIT showed absolute SMDs > 0.5 for FBG, FINS, and HOMA, with highly significant reductions in FBG and HOMA ($P < 0.01$). Compared with exercise controls, absolute SMDs for BW, FBG, FINS, and HOMA ranged 0.2–0.5, but confidence intervals were wide and crossed the null effect line.

2.4.2 Sensitivity Analysis

Sensitivity analysis for HIIT versus sedentary controls (Figure 3) and HIIT versus exercise controls (Figure 4) showed that removing any single study did not substantially alter the pooled effect sizes. Using Review Manager 5.4 to sequentially remove individual studies, overall heterogeneity remained high. Subgroup analyses based on population, modeling method, and training duration did not reveal obvious sources of heterogeneity.

2.5 Evidence Quality Evaluation

GRADE assessments (Table 5) rated the evidence quality for all outcomes (BW, FBG, HOMA) as very low across all included samples.

3. Discussion

Animal studies investigating HIIT interventions in T2DM originate primarily from China and Iran, particularly in recent years, reflecting distinct regional research patterns. The appeal of HIIT lies in its high fitness efficiency and time-saving nature, aligning with contemporary fast-paced lifestyles and fragmented time availability. Economic development and increasing competitive pressures have further driven interest in HIIT. Given the relatively high T2DM prevalence in both China and Iran [1], understanding HIIT's effects on glycemic control holds significant practical value. While animal experimental research on HIIT interventions in T2DM addresses an important applied scientific question, attention must be paid to inconsistent reporting of the same study across multiple publications.

Rodents are commonly used in exercise intervention studies for chronic diseases [39]. The included studies utilized rats or mice, but substantial heterogeneity existed in model selection, STZ concentrations, diet composition, feeding duration, and STZ injection timing. While all studies employed treadmill-based HIIT, considerable variation was observed in intensity intervals, testing methods, exercise duration, interval patterns, and weekly frequency. Notably, training duration significantly affects glycemic control outcomes. BW, FBG, FINS, and HOMA are all indirect surrogate outcomes [40] that reflect health status statically and are influenced by multiple factors including measurement timing, physiological condition, testing methods, and instrumentation. These measures show bidirectional relationships with HIIT effects, making it problematic to assess health benefits based on single-indicator changes.

Clinical studies demonstrate small effect sizes for HIIT on BW in T2DM patients, with bidirectional changes (both decreases and increases) reported [41,42]. More carefully defined exercise protocols are needed to improve evidence quality. Compared with sedentary controls, HIIT significantly reduced FBG and HOMA, demonstrating clear glycemic control effects, though no significant advantages over other exercise modalities were observed.

From a PICOS perspective, species differences, model variations, and diverse exercise protocols contributed to substantial outcome heterogeneity, reflecting considerable diversity and uncertainty across studies. These intertwined factors complicate identification of heterogeneity sources.

High-quality evidence is fundamental to realizing the value of animal experiments, and low risk of bias is essential for ensuring evidence quality. SYRCLE evaluation revealed that most included studies had unclear or high risk of bias across multiple domains. While drug intervention animal studies commonly exhibit issues with sequence generation, allocation concealment, blinding, and lack of randomized outcome assessment reporting [43], exercise intervention studies similarly show unreported or unclear sequence generation, allocation concealment, random housing, randomized outcome assessment, incomplete data reporting, and selective outcome reporting [44]. Blinding procedures remain

largely unreported or unclear.

The reproducibility crisis in experimental animal research has garnered increasing attention, with transparent reporting being key to improving reproducibility. To facilitate practical implementation, NC3Rs revised and published ARRIVE 2.0 in 2020, featuring a tiered questionnaire design with “Key 10 Items” as the basic requirement [7]. However, incomplete reporting remains problematic [45]. None of the included studies clearly described random sequence generation methods or addressed potential confounding factors. Blinding was neglected during animal grouping, intervention, and outcome assessment. While all studies reported group sample sizes ($n=$), they overlooked experimental unit design and implementation, lacked sample size justification, and underreported basic animal information [46]. Whether considering individual studies or ARRIVE 2.0 items, reporting was incomplete. Journal space limitations, absence of “negative” study publications [47], exclusive use of male animals [48], and consequences of duplicate reporting prevent full presentation of study details, resulting in poor reproducibility (<25%). Appropriate sample size calculations and effect analyses are essential [49]. The reproducibility crisis represents a major challenge for sports science research, requiring reasonable responses to align with progress in other disciplines [50].

4. Conclusion

HIIT demonstrates clear effects on blood glucose control, but the evidence is compromised by complex influencing factors, high risk of bias, poor reporting quality, substantial outcome heterogeneity, and extremely low overall evidence quality, which questions the reliability and validity of findings. We recommend using ARRIVE 2.0 as a guide to enhance research information integrity and transparency, and to improve study quality through experimental protocol registration and comprehensive reporting.

Conflict of Interest: None

Supplementary Material:

Appendix 1: PRISMA 2020 Checklist

Appendix 2: PRISMA 2020 Summary Checklist

Appendix 3: Literature Search Strategy and Document Package

Appendix 4: SYRCLE Animal Experimentation Risk of Bias Assessment Tool

Appendix 5: ARRIVE 2.0 Implementation Questionnaire

Appendix 6: Literature Screening Process

Appendix 7: All Results of Individual Studies

Appendix 8: Data and Other Available Materials

References

1. IDF Diabetes Atlas 2021. Available from: https://diabetesatlas.org/idfawp/resource-files/2021/07/IDF_{Atlas}_{10th}{Edition}_{2021}.pdf

2. Chinese Diabetes Society. Guidelines for the Prevention and Treatment of Type 2 Diabetes Mellitus in China (2020 Edition) (Part 1). Chinese Journal of Practical Internal Medicine. 2021;41(08):668-95. doi: 10.19538/j.nk2021080106
3. ACSM Fitness Trends. ACSM's Health & Fitness Journal; 2022. Available from: <https://www.acsm.org/education-resources/trending-topics-resources/acsm-fitness-trends>
4. Services USDoHaH. Physical Activity Guidelines for Americans, 2nd edition. Washington, DC: U.S. Department of Health and Human Services; 2018
5. Tan Jun, J-HT, Fei Yu, Xing Wang, Lan Zheng. Effect of High-Intensity Interval Training on Patients with Type 2 Diabetes Mellitus: An Overview of Systematic Reviews. 2021. Available from: <https://www.researchsquare.com/article/rs-457587/v1>
6. Hooijmans CR, Rovers MM, de Vries RB, et al. SYRCLE's risk of bias tool for animal studies. BMC Med Res Methodol. 2014;14:43. doi: 10.1186/1471-2288-14-43
7. Percie du Sert N, Hurst V, Ahluwalia A, et al. The ARRIVE guidelines 2.0: Updated guidelines for reporting animal research. PLoS Biol. 2020;18(7):e3000410. doi: 10.1371/journal.pbio.3000410
8. Deng Tong, Wang Yang, Huang Di, et al. Methodology for clinical practice guidelines—GRADE method theory. Chinese Journal of Evidence-Based Cardiovascular Medicine. 2018;10(12):1441-45,49
9. Deng Tong, Wang Yang, Wang Yunyun, et al. Methodology for clinical practice guidelines—Application of GRADEpro GDT in evidence grading of systematic reviews of interventional trials. Chinese Journal of Evidence-Based Cardiovascular Medicine. 2019;11(01):1-5
10. Chen X, Yang K, Jin X, et al. Bone Autophagy: A Potential Way of Exercise-Mediated Meg3/P62/Runx2 Pathway to Regulate Bone Formation in T2DM Mice. Diabetes Metab Syndr Obes Targets Ther. 2021;14:2753-64. doi: 10.2147/dmso.S299744
11. Guo Yifan. Mechanism of high-intensity interval training-induced browning of subcutaneous white adipose tissue in type 2 diabetic mice. Master dissertation. Shanghai University of Sport
12. Zhang Q, Shen F, Shen WQ, et al. High-intensity interval training attenuates ketogenic diet-induced liver fibrosis in type 2 diabetic mice by ameliorating TGF- β 1/smad signaling. Diabetes Metab Syndr Obes Targets Ther. 2020;13:4209-19. doi: 10.2147/DMSO.S275660
13. Zhang Jing. Effects of high-intensity interval training on skeletal muscle insulin resistance in type 2 diabetic mice and its mechanism. Master dissertation. Shanghai University of Sport, 2020
14. Zheng L, Rao Z, Guo Y, et al. High-Intensity Interval Training Restores Glycolipid Metabolism and Mitochondrial Function in Skeletal Muscle of Mice With Type 2 Diabetes. Front Endocrinol (Lausanne). 2020;11:561. doi: 10.3389/fendo.2020.00561
15. Zheng Lifang. Role and mechanism of lncRNA H19/miR-181a-5p axis

- in improving insulin resistance of type 2 diabetic mice by high-intensity interval training. Doctoral dissertation. Shanghai University of Sport, 2021
16. Baekkerud FH, Salerno S, Ceriotti P, et al. High Intensity Interval Training Ameliorates Mitochondrial Dysfunction in the Left Ventricle of Mice with Type 2 Diabetes. *Cardiovasc Toxicol.* 2019;19(5):422-31. doi: 10.1007/s12012-019-09514-z
 17. Zhang Qiang. Effects of exercise combined with ketogenic diet on glucose homeostasis and hepatic lipid metabolism in STZ-induced T2DM mice. Master dissertation. East China Normal University, 2017
 18. A BK, Hwan PS, Yoon Jh. Effects of Interval Training on Expression of GLUT-4mRNA and Cardiovascular Complications Cytokines in Skeletal Muscle of type 2 Diabetic Mice. *The Korean Society of Living Environmental System.* 2017;24(3):351-59. doi: 10.21086/ksles.2017.06.24.3.351
 19. Chavanelle V, Boisseau N, Otero YF, et al. Effects of high-intensity interval training and moderate-intensity continuous training on glycaemic control and skeletal muscle mitochondrial function in db/db mice. *Sci Rep.* 2017;7(1):204. doi: 10.1038/s41598-017-00276-8
 20. Rolim N, Skårdal K, Høydal M, et al. Aerobic interval training reduces inducible ventricular arrhythmias in diabetic mice after myocardial infarction. *Basic Res Cardiol.* 2015;110(4):44. doi: 10.1007/s00395-015-0502-9
 21. Stolen TO, Hoydal MA, Kemi OJ, et al. Interval Training Normalizes Cardiomyocyte Function, Diastolic Ca²⁺ Control, and SR Ca²⁺ Release Synchronicity in a Mouse Model of Diabetic Cardiomyopathy. *Circ Res.* 2009;105(6):527-47. doi: 10.1161/circresaha.109.199810
 22. Zhang Xiaofei. Different exercise modes were studied to delay renal fibrosis by influencing the protein expression of TGF- β 1 in plasma and TGF- β 1 and MMP-9/TIMP-1 in kidney during the formation of rat model type 2 diabetes mellitus. Master dissertation. Wuhan Sports University
 23. Lin S. Effects of different types of exercise preconditioning on leptin synthesis and its downstream signaling pathway in T2DM. Master dissertation. Central China Normal University, 2020
 24. Kalaki-Jouybari F, Shanaki M, Delfan M, et al. High-intensity interval training (HIIT) alleviated NAFLD feature via miR-122 induction in liver of high-fat high-fructose diet induced diabetic rats. *Arch Physiol Biochem.* 2020;126(3):242-49. doi: 10.1080/13813455.2018.1510968
 25. Khakdan S, Delfan M, Meymeh MH, et al. High-intensity interval training (HIIT) effectively enhances heart function via miR-195 dependent cardiomyopathy reduction in high-fat high-fructose diet-induced diabetic rats. *Arch Physiol Biochem.* 2020;126(3):250-57. doi: 10.1080/13813455.2018.1511599
 26. Sabouri M, Norouzi J, Zarei Y, et al. Comparing High-Intensity Interval Training (HIIT) and Continuous Training on Apelin, APJ, NO, and Cardiotrophin-1 in Cardiac Tissue of Diabetic Rats. *J Diabetes Res.* 2020;2020:1472514. doi: 10.1155/2020/1472514
 27. Yazdani F, Shahidi F, Karimi P. The effect of 8 weeks of high-intensity

- interval training and moderate-intensity continuous training on cardiac angiogenesis factor in diabetic male rats. *J Physiol Biochem.* 2020;76(2):291-99. doi: 10.1007/s13105-020-00733-5
28. Peyravi A, Yazdanpanahi N, Nayeri H, et al. The effect of endurance training with crocin consumption on the levels of MFN2 and DRP1 gene expression and glucose and insulin indices in the muscle tissue of diabetic rats. *J Food Biochem.* 2020;44(2):e13125. doi: 10.1111/jfbc.13125
29. Cai H, Chen S, Liu J, et al. An attempt to reverse cardiac lipotoxicity by aerobic interval training in a high-fat diet- and streptozotocin-induced type 2 diabetes rat model. *Diabetol Metab Syndr.* 2019;11:43. doi: 10.1186/s13098-019-0436-8
30. Mohammad P, Esfandiar KZ, Abbas S, et al. Effects of moderate-intensity continuous training and high-intensity interval training on serum levels of Resistin, Chemerin and liver enzymes in Streptozotocin-Nicotinamide induced Type-2 diabetic rats. *J Diabetes Metab Disord.* 2019;18(2):379-87. doi: 10.1007/s40200-019-00422-1
31. Amri J, Parastesh M, Sadegh M, et al. High-intensity interval training improved fasting blood glucose and lipid profiles in type 2 diabetic rats more than endurance training; possible involvement of irisin and betatrophin. *Physiol Int.* 2019;106(3):213-24. doi: 10.1556/2060.106.2019.24
32. Xing Xiaorui. Effects of high intensity interval training on insulin resistance and learning/memory function in diabetic rats. Master dissertation. Hebei Normal University, 2019
33. Li X. The effects of aerobic interval training combined with liraglutide on hepatic lipotoxicity in diabetic rats. Master dissertation. Hebei Normal University, 2018
34. Esmaeili S, Minasian V, Karami H, et al. The effects of exercise training on vascular endothelial growth factor and endostatin gene expression in cardiac tissue of rats with type 2 diabetes mellitus. *Journal of Isfahan Medical School.* 2018;36(491):909-16. doi: 10.22122/jims.v36i491.10214
35. Moghaddami K, Mohebbi H, Khalafi M, et al. The effect of interval training intensity on protein levels of ATGL and Perilipin 5 in visceral adipose tissue of type 2 diabetic male rats. *International Journal of Applied Exercise Physiology.* 2018;7(4):62-70. doi: 10.30472/ijaep.v7i4.310
36. Rahmatollahi M, Ravasi AA, Soori R, et al. Adipolin and insulin resistance response to two types of exercise training in type 2 diabetic male rats. *Iranian Journal of Endocrinology and Metabolism.* 2017;19(2):99-105
37. Alizadeh M, Asad MR, Faramarzi M, et al. Effect of Eight-Week High Intensity Interval Training on Omentin-1 Gene Expression and Insulin-Resistance in Diabetic Male Rats. *Annals of Applied Sport Science.* 2017;5(2):29-36. doi: 10.18869/acadpub.aassjournal.5.2.29
38. Martin JS, Padilla J, Jenkins NT, et al. Functional adaptations in the skeletal muscle microvasculature to endurance and interval sprint training in the type 2 diabetic OLETF rat. *J Appl Physiol.* 2012;113(8):1223-32. doi: 10.1152/japplphysiol.00823.2012
39. De Sousa RAL, Rodrigues CM, Mendes BF, et al. Physical exercise proto-

- cols in animal models of Alzheimer's disease: a systematic review. *Metab Brain Dis.* 2021;36(1):85-95. doi: 10.1007/s11011-020-00633-z
40. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines: 8. Rating the quality of evidence—indirectness. *J Clin Epidemiol.* 2011;64(12):1303-10. doi: 10.1016/j.jclinepi.2011.04.014
 41. Lora-Pozo I, Lucena-Anton D, Salazar A, et al. Anthropometric, Cardiopulmonary and Metabolic Benefits of the High-Intensity Interval Training Versus Moderate, Low-Intensity or Control for Type 2 Diabetes: Systematic Review and Meta-Analysis. *Int J Environ Res Public Health.* 2019;16(22):1-17. doi: 10.3390/ijerph16224524
 42. Han Qi, Liu Jiayi, An Nan, et al. A meta-analysis of the intervention effects of high-intensity interval training and moderate-intensity continuous exercise on glycemic control and cardiovascular risk factors in patients with type 2 diabetes. *Chinese Journal of Sports Medicine.* 2021;40(10):822-30. doi: 10.16038/j.1000-6710.2021.10.009
 43. Ferreira GS, Veening-Griffioen DH, Boon WPC, et al. Comparison of drug efficacy in two animal models of type 2 diabetes: a systematic review and meta-analysis. *Eur J Pharmacol.* 2020;879:173153. doi: 10.1016/j.ejphar.2020.173153
 44. Sun Xinzheng, Chen Xiaoke, Wang Chenghao, et al. Exercise improves pain induced by sciatic nerve injury in animal model: a Meta-analysis. *Chinese Tissue Engineering Research.* 2022;26(02):337-44
 45. Liu H, Gielen M, Bosmans J, et al. Inadequate awareness of adherence to ARRIVE guidelines, regarding reporting quality of hernia models repaired with meshes: a systematic review. *Hernia.* 2021. doi: 10.1007/s10029-020-02351-y
 46. Abbas TO, Elawad A, Pullattayil SA, et al. Quality of Reporting in Pre-clinical Urethral Tissue Engineering Studies: A Systematic Review to Assess Adherence to the ARRIVE Guidelines. *Animals (Basel).* 2021;11(8). doi: 10.3390/ani11082456
 47. Korevaar DA, Hooft L, ter Riet G. Systematic reviews and meta-analyses of preclinical studies: publication bias in laboratory animal experiments. *Lab Anim.* 2011;45(4):225-30. doi: 10.1258/la.2011.010121
 48. Massett MP, Matejka C, Kim H. Systematic Review and Meta-Analysis of Endurance Exercise Training Protocols for Mice. *Front Physiol.* 2021;12. doi: 10.3389/fphys.2021.782695
 49. Kang H. Statistical messages from ARRIVE 2.0 guidelines. *Korean J Pain.* 2021;34(1):1-3. doi: 10.3344/kjp.2021.34.1.1
 50. Zhang Liwei, Peng Fan. How does sports science cope with the replicability crisis? *Journal of Sports Research.* 2021;35(06):1-11. doi: 10.15877/j.cnki.nsic.20211011.001

Note: Figure translations are in progress. See original paper for figures.

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