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Non-pharmacological interventions for the prevention of type 2 diabetes in low income and middle-income countries: a systematic review of randomized controlled trials

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Title: Non-pharmacological interventions for the prevention of type 2 diabetes in low income and middle-income countries: a systematic review of randomized controlled trials

Running title: T2DM Prevention in LMICs

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Abstract

Objective: Diabetes poses serious health threats and economic burdens to patients, especially in Low income and -Middle-Income Countries (LMICs). The increasing trend of diabetes can be prevented by lifestyle modifications, a healthy diet, exercise, etc. This systematic review searches for non-pharmacological interventions for the prevention of T2DM among non-diabetic and prediabetes patients from LMICs.

Settings: Low income and -Middle-Income Countries

Participants: Adult population aged over 18 years without having diabetes.

Primary and secondary outcome measures: Primary outcome is to measure the change of incidence of type 2 diabetes mellitus. The secondary outcome is to measure changes of HbA1c level, weight/BMI, fasting glucose level, 2-h glucose from baseline of the included randomized controlled trials.

Methods: This review has been conducted following the standard systematic review guidelines. A total of six electronic databases including Medline, Embase, the Cochrane Library, Web of Science, ClinicalTrials.gov, and ICTRP were searched using a comprehensive search strategy.

Two sets of independent reviewers performed screening, quality appraisals, and data extraction. Narrative coalescence of selected articles was demonstrated using tables. No meta-analysis was performed due to the lack of homogenous intervention strategies and study settings.

Result: A total of 5 studies were included for the review with a combined population of 1,734 from three countries. Three of the studies showed a significant reduction of T2DM incidence after the intervention of physical training and dietary modifications. Four of the studies also demonstrated a significant reduction of different secondary outcomes like weight, body mass index, fasting & 2-h plasma glucose, and HbA1C. All the studies demonstrated a low risk of bias in most of the bias assessment domains with some unclear results in allocation concealments.

Conclusions: Emphasizing non-pharmacological interventions for T2DM prevention can improve health outcomes and lessen the economic burdens, which will be of paramount importance in LMICs.

PROSPERO registration: CRD42020191507

Keywords: Non-pharmacological, Prevention, T2DM

Strengths and limitations of this study

- The methodological rigor following PRISMA guidelines is the major strength of this systematic review.
- The prime strength of this systematic review is the inclusion of RCTs only, which helped to ensure the true effectiveness of the intervention programs
- We included articles published in English only which might have missed some potential articles published in other languages.
- Trials conducted only in India, Iran, and China fulfilled the selection criteria and were included in the review. Therefore, the interpretation might not be socially and culturally applicable for other LMICs.
- A meta-analysis could not be conducted due to the heterogeneity of the included articles.

Introduction

Diabetes mellitus is a group of metabolic disorders marked by excessive serum glucose levels caused by insufficient insulin secretion, insulin action, or both. Type 2 diabetes mellitus (T2DM) is the most prevalent form of diabetes, which accounts for 90 to 95 percent of all diabetes cases. It occurs when insulin secretion is insufficient to overcome an underlying abnormality of increased insulin resistance.[1]

Diabetes is linked to a number of adverse health outcomes. It increases the risk of cardiovascular disease and stroke significantly. In reality, most diabetic patients die of cardiovascular complications. In 2017, diabetes has risen to the 10th spot on the Institute for Health Metrics and Evaluation (IHME) global cause of death list,[2] but it directly or indirectly contributes to the other top causes of death like coronary heart disease (CHD) and stroke. Diabetic microvascular complications are the major cause of blindness, renal failure, and nontraumatic amputations.

T2DM incidence has seen a rapid global increase during the past few decades. Diabetes prevalence in the world among adults over the age of 18 increased to 8.5 percent in 2014 from 4.7 percent in 1980.[3] Diabetes affects more than 420 million individuals globally today. By 2030, this number is expected to reach 570 million, and by 2045, 700 million.[4] The burden of diabetes in terms of prevalence, incidence, Disability-Adjusted Life Years (DALYs), and death is predicted to continue to rise from 2018 to 2025.[5] The economic burden of diabetes is monumental but is usually largely overlooked. For instance, in 2019, direct and indirect medical and treatment expenses, as well as expenditures associated with diabetes-related disability and mortality exceeded $760 billion which is around 10% of total health expenditure on adults.[6, 7] This trend of economic burden is predicted to continue its upward trend.[8] Because diabetes has no cure, it is essential to focus on primary prevention via food and lifestyle changes.[1]

Uncontrolled T2DM can lead to blindness, renal failure, heart disease, and other severe complications. There is a period before diabetes is diagnosed in which blood glucose levels are elevated but not elevated enough to be labelled as diabetes. Prediabetes is the medical term for this condition.[9] It is estimated that one in every 13 adults aged 20 to 79 years has impaired glucose tolerance which amounts to 463 million people.[6] According to estimates, up to 70% of those with prediabetes progress to develop T2DM. Fortunately, advancing from prediabetes to diabetes isn't

a foregone conclusion.[10] The preventability of diabetes has been demonstrated by several randomized trials.

Early management in the prediabetes stage is beneficial to decrease diabetes development and related consequences since T2DM is a chronic illness with progressive impairment in glucose metabolism resulting in various systemic complications. Strong epidemiologic evidence indicates that diabetes is associated with lifestyle. The non-randomized Malmö study indicated that a lifestyle program for the prevention of T2DM in persons with impaired glucose tolerance is feasible.[11] Previously, randomized intervention studies showed that changes in diet and physical activity can delay or even prevent the onset of T2DM in persons with impaired glucose tolerance.[12-15] Studies in high-risk groups other than persons with impaired glucose tolerance have also been conducted. A Norwegian lifestyle intervention indicated a beneficial impact of diet and exercise on insulin sensitivity in people with several cardiovascular risk factors.[16]

A systematic literature review conducted in 2010 evaluated four cohort studies and found that the incidence of T2DM can be reduced by 28–59% by lifestyle changes.[17] A meta-analysis backs up this claim, estimating that to prevent or delay each case of diabetes, 6.4 (95% CI: 5.0–8.4) people would need to be treated through lifestyle intervention. Weight loss diets (low fat, high protein, or the Mediterranean) appear to be helpful, but every one of them has drawbacks that necessitate careful food selection. Evidence also indicates that weight reduction maintenance strategy demands frequent exercise.[17]

More than three-quarters of the people suffering from diabetes are from low- and middle-income countries (LMICs), and diabetes prevalence is expected to rise fastest in these countries.[18] Diabetes prevalence estimates in LMICs have largely relied on self-reporting, which might have vastly understated the true prevalence of T2DM in countries lacking robust screening protocols and access to care.[19] However, In LMICs, there has been relatively little effort to adopt preventive programs and delivery approaches for T2DM.[20] Evidently, no such programs from these regions were found in a relatively fresh systematic review of 38 real-world diabetes preventive trials.[21] Given the significant differences in health systems, resources, culture, and lifestyle risk factors among LMICs, this creates a significant evidence gap. To reiterate the fact, context-specific evidence is necessary and recommended, because the burden of diabetes will proportionately decrease with the narrowing of the evidence-to-action gap. It will also lead to lowering of death

rates as well as lower healthcare expenditures.[22-24] This systematic review seeks to evaluate the effectiveness of the non-pharmacological programs for the prevention of T2DM conducted in LMICs to address that knowledge gap.

Methods

This systematic review was conducted using the Cochrane systematic review norms [25] And PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) recommendations.[25, 26] The systematic review is registered in the International Prospective Register of Systematic Reviews (Registration number: CRD42020191507). The protocol outlines the approach in-depth, including the development of the search strategy, double-screening, double-data extraction, double-quality assessment of included articles, and narrative synthesis.[27] A detailed search strategy was constructed using the keywords including as Exercise, "Physical activity", ''Nutritional therapy'', ''Meal plan'', "Weight loss", "Lifestyle change", "Lifestyle modification", Diabetes, "Diabetes mellitus", ''Type 2 diabetes mellitus'', T2DM, DM, LMICs, "Developing country", "Peri-urban'', urban, rural to search different electronic bibliographic database including Medline through PubMed, Embase, the Cochrane Library (Cochrane Central Register of Controlled Trials- CENTRAL), Web of Science, ClinicalTrials.gov, ICTRP, etc. The search period covered from the inception of the databases to February 2021. Non-pharmacological interventions on non-diabetic adult populations in LMICs were included in randomized control trials. Two reviewers independently screened the "title and abstract" and "full text" of the retrieved articles, and any disagreements were resolved by a third reviewer. To keep track of the screening process, reference management software "Rayyan" was used. Each study was evaluated critically for the possibility of risk of bias (ROB). A narrative synthesis of study participant characteristics and intervention categories with specific primary and secondary outcomes was demonstrated. The risk ratio (RR) of diabetes mellitus status was recorded from baseline and end line information. Mean and standard deviation of secondary outcomes (Change in weight, BMI, and fasting blood glucose level) were recorded from both the control and intervention groups.

In terms of interventions, study duration, and study settings, the included studies were too heterogeneous to be included in the meta-analysis. A narrative synthesis was performed as a substitute for a meta-analysis. We were not able to conduct a subgroup analysis or a sensitivity analysis for the same reason. In this systematic review, we did not observe the publication bias

because we were not able to perform the meta-analysis. Funnel plots are generally used to estimate the risk of publication bias. It is also recommended in different studies to avoid a test of funnel plot asymmetry or the existence of publication bias if the number of selected studies is less than 10 in a meta-analysis.[28]

Patient and public involvement

Patients or the public were not involved in the design, conduct, reporting, or dissemination plans of our research.

Results

A thorough search of the literature in the selected databases using the search strategy resulted in the retrieval of 2,737 articles. A total of 2,592 articles were finally listed for the title and abstract screening after removing 145 duplicates. A total of 25 articles were selected following employing the inclusion and exclusion criteria for the full-text review.

Figure 1: Systematic review PRISMA flow diagram

We were unable to find the full text of only one article, even after communicating with the authors. The article was published in 1984, and we excluded it from our full-text review due to unavailability. The Da Qing IGT and diabetes study[12] fulfilled all the inclusion criteria, but we decided to leave the article out of our review since it used the 1985 World Health Organization (WHO) criteria to define IGT and diabetes patients. The criteria were updated in 1999. Currently, WHO[29], ADA[30], and Diabetes UK[31]- all use the same diagnostic criteria, and all our included studies follow this guideline for diagnosis of diabetes and IGT. As a result, the interpretations from the Da Qing study could be potentially misleading when compared to the other selected recent studies.[32] Finally, after the full-text review, 5 articles were included for analysis. Figure 1 shows the PRISMA flow diagram of the inclusion process. Supplementary table 1 is provided containing the list of 20 selected articles that did not fulfill inclusion criteria and were eventually excluded, along with the reasons for exclusion.

Five articles from three geographic regions with a combined sample of 1,734 were included for final analysis. The basic characteristics of these selected articles are given in Table 1.

Table 1 Attributes of studies included.

Author	Year of Publication	Sample size	Study design	Country	Age in Year	Gender	Intervention	Baseline Diabetes Status of the participants	Baseline BMI (kg/m^2)
Kavumpurathu R. Thankappan et al[33]	2018	Total- 1007 Intervention- 500 Control- 507	Cluster RCT	India	30-60	M and F	Peer-support lifestyle intervention	Non-diabetic	Not measured
Xia Dai et al[34]	2019	Total- 172 AT- 34 RT- 31 AT+RT- 37 Control- 35	RCT	China	55-75	M and F	1. Aerobic training (AT), 2. Resistance training (RT), 3. Both AT and RT	Pre-diabetic	Not measured
Arpana Gaddam et al[35]	2015	Total Sample- 140 Intervention- 74 Control- 66	Parallel RCT, single blind	India	30-70	M and F	Fenugreek powder, 5 g with 200 ml water twice a day before meals and physical activity+ diet	IFG or IGT	Control: 25.95 ± 3.04 Intervention: 26.62 ± 2.82
Shaahin Shahbazi et al[36]	2017	Total- 336 NFD- 112 HMD- 112 Control- 112	Parallel RCT	Iran	>20	M and F	1. HMD 2. NFD	Prediabetic	Presented categorically
Zidu Xu et al[37]	2020	Total-79 Intervention- 41 Control- 38	RCT	China	23-67	M and F	Mobile-based intervention+ behavioral theory	High risk of diabetes	Control: 24.7 (23.4-26.1) Intervention: 25.3 (24.7-26.2)

AT- Aerobic training, F-Female, HMD- High-monounsaturated fat diet, M- Male, NFD- Normal fat diet, RCT- Randomized Control Trial, RT- Resistance training

All the studies were recent publications, dating from 2015 to 2020. India and China both were the sites of two studies each. The Rest was conducted in Iran. Two of the five studies were randomized control trials, two were parallel randomized control trials, and the rest was cluster randomized control trial. The period of the intervention varied from six months to 36 months. Participants' age in the selected studies ranged from more than 20 years to 75 years. All of the studies had both male and female subjects as participants. The five studies used completely different intervention methods, such as peer-support lifestyle intervention,[33] Aerobic, and resistant physical training,[34] Fenugreek powder,[35] High-monounsaturated fat diet,[36] and mobile-based intervention, and behavioral theory.[37] Supplementary table 2 details the selection criteria and interventions used in each of the selected articles. All the studies depicted the efficiency of the intervention in terms of the prevention of T2DM. Four of them used participants' diabetes status as the primary outcome. One study used changes in dietary behaviors and physical activity as the main outcome. The primary outcome, diabetes status, was measured by Oral Glucose Tolerance Test (OGTT) following the American Diabetes Association (ADA) criteria in three studies.[33-35] And one study uses fasting glucose level or 2-h post-glucose challenge following the ADA criteria.[36]

Table 2 shows the summary findings of the primary outcome and Table 3 and Table 4 demonstrate the secondary outcomes of the included studies. Kavumpurathu and the team evaluated the impact of peer-support lifestyle intervention to reduce the incidence of T2DM. After 12 months of intervention, the incidence of T2DM was 14.9% and 17.1% in the intervention and the control group respectively (Relative Risk: 0.88, 95% CI 0.66–1.16, p = 0.36) (Table 2). The secondary outcomes also showed improvement in the intervention groups, but it was not found to be statistically significant. Xia Dai et al examined the effect of physical training on T2DM. The intervention group had three arms, resistance training (RT), aerobic training (AT), and a combination of both (RT+AT). After 24 months of intervention, all the intervention arms showed lower cumulative incidence than the control group (22%, 26%, 21%, and 69% for the aerobic, resistance, combined, and control groups, correspondingly). The age and sex-adjusted hazard ratios were 0.26 (95% CI, 0.11-0.62) in the combined group, 0.35 (95% CI, 0.15-0.79) in the resistance group, and 0.28 (95% CI, 0.13- 0.64) in the aerobic group. Among the secondary outcomes, the intervention arms showed a significant reduction in 2-h plasma glucose level, HbA1C level (Table 3) and weight (Table 4) than the control group. The trial conducted by Arpana Gaddam et al determined the effect of Fenugreek to avert the development of T2DM in people

who are prediabetic. After following the intervention and the control group for 36 months, the incidence of T2DM was found to be 18.8% and 55.7% respectively. Relative risk reduction was 0.6 (p <0.01). There was also a significant reduction of fasting and 2-h plasma glucose levels.

Table 2: Summary findings of primary/ main outcome of the selected studies

Author	Duration of Intervention (months)	Primary Outcome: Diabetes Status				Risk Ratio (95% CI) *P*- value	Measurement of Primary Outcome
		Intervention		Control			
		Baseline (%)	End line (%)	Baseline (%)	End line (%)		
Kavumpurathu R. Thankappan et al[33]	12	0/500	68/456 (14.91%)	0/507	79/463 (17.06%)	0.88 (0.66– 1.16) *P*= 0.36	OGTT according to the ADA criteria
Xia Dai et al[34]	24	AT: 0/ 34 RT: 0/31 AT+RT: 0/37	Cumulative Incidence: AT: 22% RT: 26% AT+RT: 21%	0/35	Cumulative Incidence: 69%	Hazard Ratio: AT: 0.28 (0.13- 0.64) RT: 0.35 (0.15- 0.79) AT+RT: 0.26 (0.11- 0.62)	OGTT according to the ADA criteria
Arpana Gaddam et al[35]	36	0/ 74	Cumulative Incidence: 17/74 (22.97%)	0/ 66	Cumulative Incidence: 34/61 (55.74%)	RRR: 0.6 *P* < 0.01	OGTT
Shaahin Shahbazi[36]	24	HMD: 0/112 NFD: 0/112	HMD: 10/107 (9.35%) NFD: 14/ 106 (13.21%)	0/112	20/109 (18.35%)	HMD: 0.43 (0.1–0.9) *P* = 0.03 NFD: 0.60 (0.2–1.2) *P* = 0.1	Fasting state or 2-h post glucose challenge according to the ADA criteria
Zidu Xu et al[37]	6		-	-	-	-	Changes in dietary behaviors and physical activity

ADA- American Diabetes Association, AT- Aerobic training, HMD- High-monounsaturated fat diet, NFD- Normal fat diet, OGTT- Oral glucose tolerance test, RRR- Relative Risk Reduction, RT- Resistance training, 95% CI (95% confidence interval)

Shahbazi et al explored the outcomes of a fat diet without a weight-loss program on preventing or delaying the onset of T2DM in subjects with either impaired fasting glucose or impaired glucose tolerance. The intervention group had two arms, a high-monounsaturated fat diet (HMD), and a normal fat diet (NFD). After 24 months of intervention, the incidence of T2DM was 9.4%, 13.2%, and 18.4% in HMD, NFD, and control groups respectively.

Table 3. Summary findings of secondary outcomes of the included studies (Fasting Glucose, 2 hours after plasma glucose, HbA1c)

Author	Secondary Outcomes								
	Fasting Glucose Level			2-h Plasma Glucose			HbA1c (%)		
	Intervention	Control		Intervention	Control		Intervention	Control	
	Mean (mmol/L)/ Mean Change ± SD	Mean (mmol/L)/ Mean Change ± SD	*P*-value	Mean (mmol/L)/ Mean Change ± SD	Mean (mmol/L)/ Mean Change ± SD	*P*-value	Mean/ Mean Change ± SD	Mean/ Mean Change ± SD	*P*-value
Kavumpurathu R. Thankappan et al[33]	0.225 ± 0.811	0.23 ± 0.988	0.79	0.43 ± 1.97	0.47 ± 2.11	0.63	-0.003 ± 0.43	0.056 ± 0.603	0.08
Xia Dai et al[34]	AT: 5.40 ± 0.56 RT: 5.52 ± 0.57 AT+RT: 5.08 ± 0.46	6.59 ± 0.57	-	AT: 7.48 ± 1.37 RT: 7.17 ± 1.31 AT+RT: 6.85 ± 1.78	8.26 ± 0.97	0.007	AT: 5.89 ± 0.39 RT: 5.46 ± 0.50 AT+RT: 5.52 ± 0.46	6.53 ± 0.75	<0.001
Arpana Gaddam et al[35]	Mean: 99.7 ± 11.4	Mean: 100.6 ± 11.04	<0.005	Mean: 129 ± 29.6	Mean:147.3 ± 32.6	<0.01	-	-	-
Shaahin Shahbazi[36]	HMD: −1.6 ± 8.2 NFD: −1.4 ± 7.9	4.3 ± 10.7	0.001	HMD: −3.9 ± 16.5 NFD: −0.6 ± 17.7	3.3 ± 14.8	0.005	-	-	-

AT- Aerobic training, BMI- Body Mass Index, CI- Confidence interval, HMD- High-monounsaturated fat diet, NFD- Normal fat diet, RT- Resistance training, SD- Standard deviation, NS- non-significant

Relative risk in HMD arm was 0.43 (95% CI, 0.1–0.9; P = 0.03), and in the NFD arm was 0.60; (95% CI, 0.2–1.2; P = 0.1). HMD and NFD arms were also shown to be effective in reducing the fasting and 2-h plasma glucose level significantly. Zidu Xu et al tested a Mobile-based intervention plus behavioral therapy to affect dietary behaviors and physical activity among the population at high risk of T2DM. The control group received the same intervention through printed material. After 6 months of intervention, the intervention group showed higher reduction of BMI [3 months- 24.1 (23.5-25.2), 6 months- 23.2(22.7-24.3)] than the control group [3 months- 24.1(23.3-25.6), 6 months- 24.2(22.8-25.6)] when compared to 3-month intervention data.

Table 4: Summary findings of secondary outcomes of the included studies (Weight, BMI)

Author	Secondary Outcomes					
	Weight			BMI (kg/m²)		
	Intervention	Control		Intervention	Control	
	Mean (Kg)/ Mean Change ± SD	Mean(Kg)/ Mean Change ± SD	*P*-value	Mean/ Mean Change ± SD	Mean/ Mean Change ± SD	*P*-value
Kavumpurathu R. Thankappan et al[33]	1.22 ± 3.27	1.24± 2.91	0.95	-	-	-
Xia Dai et al[34]	AT: 57.92 ± 8.50 RT: 58.35 ± 7.73 AT+RT: 58.04 ± 7.25	65.74 ± 7.66	<0.001	-	-	-
Arpana Gaddam et al[35]	Mean: 68.79 ± 8.43	Mean: 68.34 ± 10.1	-	Mean: 26.43 ± 3.00	Mean: 25.91 ± 3.38	NS
Shaahin Shahbazi[36]	HMD: −0.1 ± 0.7 NFD: −0.09 ± 0.6	0.2 ± 2.1	0.07	-	-	-
Zidu Xu et al[37]	-	-	-	At 3 months- 24.1 (23.5-25.2) At 6 months- 23.2 (22.7-24.3)	At 3 months- 24.1 (23.3-25.6) At 6 months- 24.2 (22.8-25.6)	<0.001

AT- Aerobic training, BMI- Body Mass Index, CI- Confidence interval, HMD- High-monounsaturated fat diet, NFD- Normal fat diet, RT- Resistance training, SD- Standard deviation

* p-value indicates group-time interaction, and it denotes the significant difference among comparison groups over the intervention time period.

The quality of the included RCTs was assessed applying the Cochrane Risk of Bias tool. Two authors assessed the studies independently and then cross-checked the result among themselves. They warranted the judgment of the senior author to resolve some disagreement and finally came up with a combined result with consensus. Figure 2 provides a graphical demonstration of the risk of bias of the studies.

Figure 2: Risk of Bias assessment of included studies

Random sequence generation of all included studies presents a low risk of bias. Four studies[33-35, 37] used a randomization list generated by a computerized program whereas one study[36] used block randomization to minimize the selection bias. Allocation of the included studies was concealed in two studies[34, 35] through assigning a unique code and in opaque and numbered envelopes. Thus, it presents a low risk of bias for 40% of the studies whereas 60% of studies[33, 36, 37] represent an unclear risk of bias in this section. All the included studies reported their primary and secondary outcome according to their objective through which low risk of bias was reported against selective bias. One of the studies was triple blinded study[33] whereas because of the characteristics of the study, respondents were not required to be blinded in another study.[37] Two studies did not mention anything about performance bias.[34, 36] However, the study conducted by Gaddam et al.[35] portrayed a high risk of bias. Detection bias was assessed as low in four studies and unclear in one which was opposite during assessing other biases (Low in one study and unclear among four). 80% of studies (Four) mentioned the data related to attrition or loss to follow-up. Thus, they were assessed with a low risk of bias. However, one study (20%)[34] assessed with a high risk of bias as it conducted per-protocol analysis having a high attrition rate. Figure 2 graphically demonstrates the ROB domains with corresponding assessment.

Discussions

The goal of this systematic review is to assess the effectiveness of non-pharmacological interventions in lowering the prevalence of T2DM in low- and middle-income countries. For this purpose, we undertook a comprehensive search strategy to screen 2,737 articles to finally select included five randomized control trials with a total population size of 1,734, spanning over the last six years, and conducted in three countries. The lack of older studies highlights the fact that non-pharmacological diabetes prevention strategies are a relatively new concept but are gaining

attention lately. These trials assessed different intervention strategies like lifestyle intervention, physical training, and dietary intervention on normal or prediabetes patients. As there was no more than one study that used the same intervention strategy, no meta-analysis could be performed.

Our primary outcome was the incidence of T2DM, which was measured in the studies by assessing the OGTT or fasting glucose level and 2-h glucose challenge according to the ADA[30] or WHO[29] criteria at baseline and end-line evaluation. Among the secondary outcomes, we measured weight, BMI, fasting & 2-h glucose level, and HbA1C level to assess the effectiveness of the intervention programs.

Two studies used lifestyle intervention to reduce diabetes incidence. One used peer support, and the other study used a mobile-based app to deliver the intervention. Studies showed that lifestyle intervention lessons can lessen the probability of a person becoming diabetic.[38] The peer-support study used sittings organized by professionals and then by non-professional peer leaders to deliver the lifestyle intervention knowledge among the participants. The control group received only informational booklets. The mobile-based intervention study used mobile-app-based push notifications to deliver messages on improving dietary behaviors, physical activity, etc. The first study found a decrease in diabetes incidence after the intervention period. But the result was not statistically significant. The second study used a different primary outcome, but among the secondary outcomes, it found a significant decrease in BMI between two points of the intervention.

The efficacy of dietary modification or intervention was measured in two studies. One used Fenugreek powder for its hypothesized effect on glucose homeostasis,[39-43] and the other study used an HMD and NFD regimen to elucidate the effect of dietary modification. The ADA recommends that having the right amount of monounsaturated fat in the diet helps prevent T2DM.[44] The first study administered 5 g debittered, defatted Fenugreek powder with 200 ml water before meal two times a day for three years and found a significant decrease in relative risk for T2DM in the intervention group. They also observed a significant reduction in fasting and two-hour plasma sugar level in the intervention group. The second study contrasted an HMD and NFD group with the control group. The control group followed the USDA Food Pyramid Guide for diet. The study offered no explanation of using a US guideline in LMICs. It can be assumed that they used this guideline to simply encourage the participants to reduce their fat intake to less than 30% of energy consumption and saturated fat to less than 10% of total energy. After the intervention, the HMD

section saw the most significant decrease in the incidence of diabetes compared with the NFD and non-intervention group. The cumulative incidence also showed a marked reduction in the HFD arm.

Only one study evaluating the efficacy of supervised physical training to reduce the risk of T2DM was included in the review. This study had three intervention arms, resistance training, aerobic training, and both resistance and aerobic training. The control group was encouraged to follow normal daily activities. After two years of intervention, it demonstrated a higher cumulative incidence in the control group than the intervention group with a significant hazard ratio. Among the arms, the combined physical training arm showed greater efficacy in diabetes risk reduction, followed by the aerobic training arm. Both the studies using Fenugreek and exercise as interventions[34, 35] were conducted among prediabetic participants and reported cumulative incidence of diabetes after the intervention period. This resulted in a much higher proportion of controls ending up as diabetic (69% and 55.74% respectively) which, however, was consistent with previous findings.[45] A joint position statement from the American College of Sports Medicine and the American Diabetes Association demonstrated the effectiveness of physical activity and physical training, especially the combination of both aerobic and resistance training.[46]

In terms of the effectiveness, it is difficult to compare the different intervention methods due to the lack of a uniform approach of the selected studies in measuring the impact. However, exercise and dietary interventions[34-36] showed more significant results than lifestyle alone[33] in preventing the onset of T2DM, reducing body weight, and decreasing fasting glucose level. We did not find any trial comparing the effectiveness of lifestyle, exercise, and dietary interventions conducted in LMICs. Three of the selected studies[33, 35, 37] considered cultural aspects of the participants while designing the appropriate intervention. It was previously reported that culturally tailored and targeted interventions yield better results than a generalized approach to prevent diabetes.[47, 48] We also think that the distinctive difference in lifestyle, food habit, and healthcare-seeking behavior between people living in LMICs and HICs warrant specifically-aimed interventions. This is the principal reason we explicitly chose LMICs as the place of studies to be included in this review.

We tried to broaden the reach of the review by conducting a comprehensive search in several databases but limited our searches to the English language only. There might be other studies in local languages other than English which we have missed in our search. This is one of the main

limitations of our review. There were several studies conducted in other LMICs on nonpharmacological interventions for T2DM, but they were either conducted on diabetic patients, or had different primary outcomes, or on younger respondents, and so on. At the time of our search, we only found studies from Iran, China, and India that met all the inclusion criteria and were included in the systematic review. Besides, many urban settings in China are not economically different from metropolitan areas in most HIC's. This fact underscores the need for further randomized controlled trials for the non-pharmacological interventions of T2DM to be conducted in LMICs. As the selected studies used different parameters and attributes to measure the primary outcome, and they have different intervention periods, it is difficult to have an exact comparison among the studies regarding the best strategy and duration of the interventions.

The principal strength of this systematic review is the inclusion of RCTs only, which helped to ensure the true effectiveness of the intervention programs. We also followed the Cochrane guideline for systematic review stringently, which also ensured the high quality of the review. All the studies demonstrated low ROB in most of the bias assessments. There were some unclear results in allocation concealments and other biases. Four of the five studies used the same primary outcome, but all five studies used different intervention methods. The studies used a sufficient intervention period, but no crossover trials were found.

Future research should examine the efficacy of diverse non-pharmacological approaches for diabetes prevention programs. These researches must adapt culturally and geographically appropriate intervention measures for LMICs to maximize their effectiveness in both clinical and community settings. Policymakers and healthcare stakeholders from LMICs should formulate health policies to mobilize resources to emphasize the non-pharmacological interventions for T2DM. Resources for diabetes prevention programs should be focused to enhance the ability to reach diverse adults and young adults at risk for type 2 diabetes.

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Authors' contributions: KMSUR conceptualized the review. AS, RD, SE, and MSI screened the articles, extracted data, and assessed the risk of bias. KMSUR resolved the conflicts in screening, data extraction, and assessment of risk of bias. AS, RD, SE, MSI and KMSUR drafted the manuscript. KMSUR reviewed, revised, and finalized the manuscript. All the authors approved the final version of the manuscript.

Conflict of interest

As for the publishing of this paper, the authors declare no conflict of interest.

Ethical approval and consent for publication

This is a systematic review incorporating published articles. No ethical approval is required. There was no involvement of any participants.

The name of the institutional Ethics Committee that approved the research: Not applicable

The approval number: Not applicable

The date of the approval: Not applicable

Data sharing statement

The datasets generated and/or analyzed during this review shall be available from the corresponding author on reasonable request.

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Supporting information:

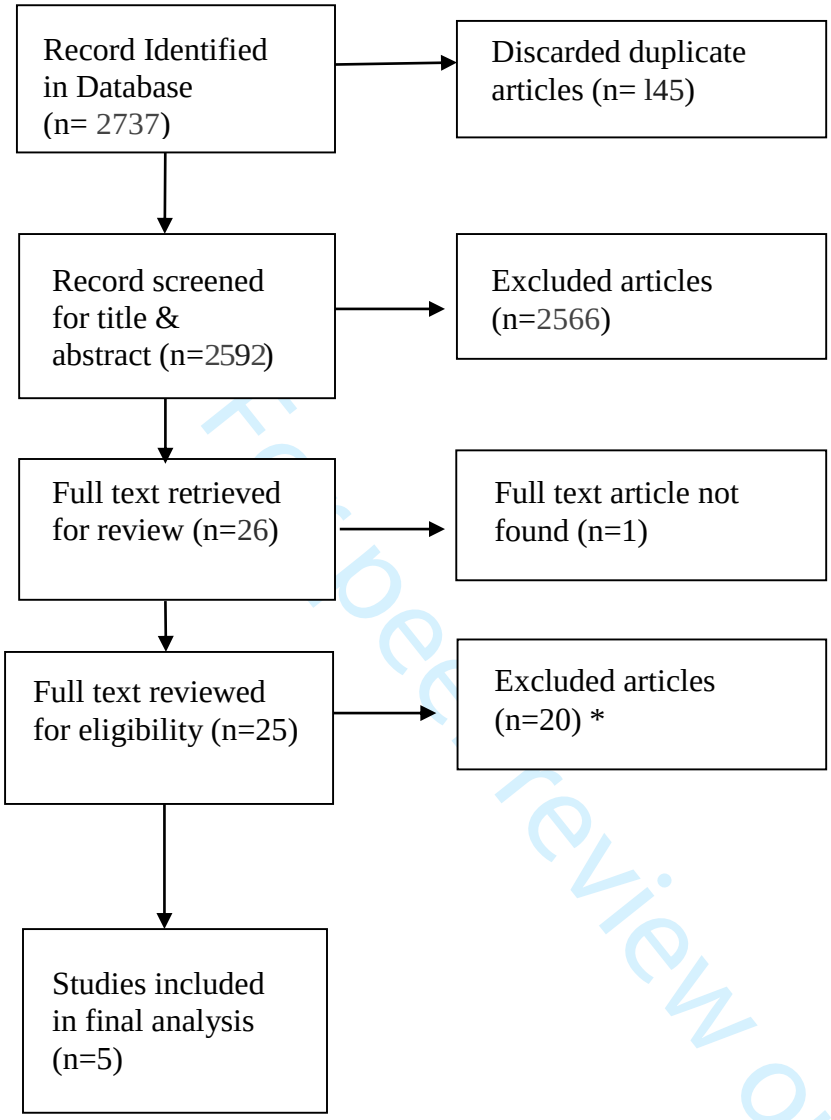
Supplementary Table 1: List of excluded articles

Supplementary Table 2. Selection criteria and interventions used by the included studies

Figure legends

Figure 1. Systematic review PRISMA flow diagram

Figure 2. Risk of Bias assessment of included studies



*Causes of exclusion: Not in LMICs= 15; Not focusing on prevention of DM = 1; Intervention provided on GDM population = 1; Not on adult = 1 Pharmacological intervention=1; Used older (WHO) criteria to define IGT and diabetes patients = 1

Figure 1: Systematic review PRISMA flow diagram

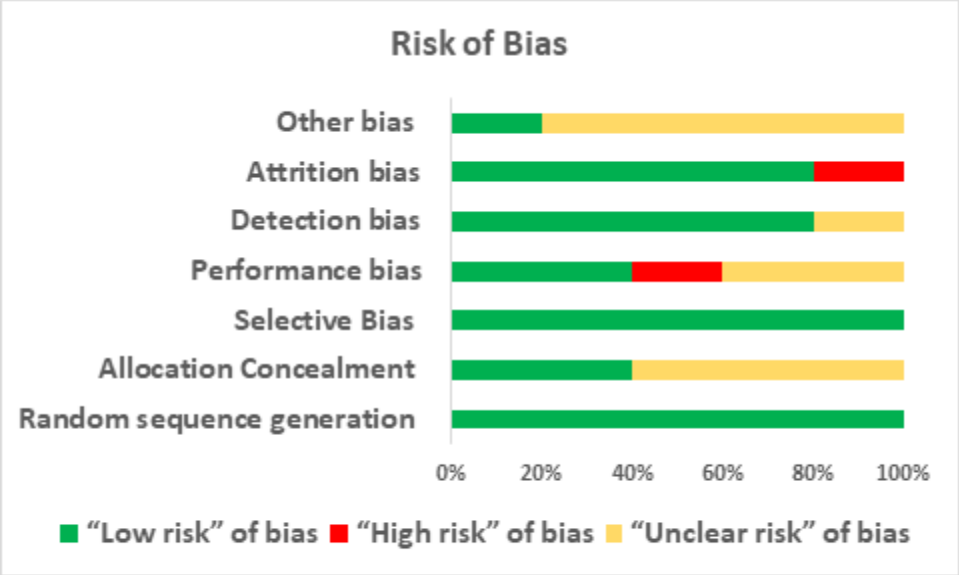


Figure 2: Risk of Bias assessment of included studies

Supplementary Table: List of excluded articles

Serial no.	Author	Exclusion Criteria
1	J.A. Dunbar et al	Outside LMIC
2	Gang Hu et al	Population: GDM
3	Elroy J. Aguiar et al	Outside LMIC
4	Jessica E. Bourne et al	Outside LMIC
5	Yoshimi Fukuoka et al	Outside LMIC
6	J. Genz et al	Outside LMIC
7	Diabetes Prevention Program Research Group	Primary outcome: cost effectiveness
8	Jeffrey A. Katula et al	Outside LMIC
9	SoJung Lee et al	Outside LMIC, Population: age group 12-18years
10	Vegard Nilsen et al	Outside LMIC
11	Matthew J. O'Brien et al	Outside LMIC
12	Matthew J. O'Brien et al	Outside LMIC
13	V Ponzo et al	Outside LMIC
14	Ayman Bani Salameh et al	Population: age group 12-18y
15	Roberto P. Treviño et al	Outside LMIC, Population: 4th Grade children
16	Jaakko Tuomilehto et al	Outside LMIC
17	Katya Vargas-Ortiz et al	Control and Intervention both received Metformin
18	Peter Wein et al	Outside LMIC, Population: GDM
19	Sara Engel et al	Outside LMIC
20	Da Qing et al	Used older (WHO) criteria to define IGT and diabetes patients

GDM- Gestational Diabetes Mellitus, LMIC- Low- and middle- income- countries

Supplementary Table 2. Selection criteria and interventions used by the included studies

Author	Selection Criteria	Interventions used
Kavumpurathu R. Thankappan et al	i. No history of diabetes or other chronic illness that might affect their participation in the trial, ii. Being literate in the local language (Malayalam), iii. Not being pregnant, iv. Not taking medications known to affect glucose tolerance (glucocorticoids, antiretroviral drugs and antipsychotics) v. IDRS ≥ 60	12-month community-based peer-support program comprising 15 group sessions (12 of which were led by trained lay peer leaders) and a range of community activities to support lifestyle change.
Xia Dai et al	i. Adults aged 55 to 75 years ii. Diagnosis of prediabetes (5.6≤ fasting plasma glucose [FPG] <7.0 mmol/L and/or 7.8≤ 2-h glucose [2hPG] <11.1 mmol/L and/or 5.7%≤ haemoglobin A1c [HbA1c] <6.4%) iii. tested muscle strength more than or equal to level 4 and the ability to participate in the study timeline.	1-hour dietary class with a dietitian and a 1-hour exercise training class. 3 intervention groups selected by assigning computer-generated random numbers: i. Aerobic Training: Aerobic dancing designed by self-developed diabetes quantitative exercise prescription. ii. Resistance training: major muscle group exercises such as leg presses, leg extensions, chest presses, pull downs, rowing, and shoulder presses. iii. Combined training: 30 minutes of resistance training for three non-consecutive days per week, immediately following 30 minutes of aerobic training.

Arpana Gaddam et al	i. Men and women aged between 30–70 years ii. Body Mass Index (BMI) ≥ 19 kg/m2, iii. Fasting plasma glucose (FPG) 100–125 mg/dl (IFG) (or) post 75 g oral glucose load, plasma glucose (oral glucose tolerance test, OGTT) 140–199 mg/dl (IGT) iv. Those who were willing to give informed consent form	Debitterized, defatted and deodorized Fenugreek fiber with vitamins, minerals and amino acids supplied by an Indian pharmaceutical industry- 5 g twice a day, was given to the intervention group along with 200 ml of water half an hour before meals and they were asked to follow the same dosage regime up to the end of study.
Shaahin Shahbazi et al	Fasting glucose level of 100–125 mg/dL (5.6–6.9 mmol/L) or a 2-h post-glucose challenge in the range of 140–199 mg/dL (7.8–11.0 mmol/L), confirmed by two tests.	i. High-monounsaturated fat diet (HMD): 15% from protein, 45% from fat (25% MUFA, 10% PUFA, 10% SFA), and 40% from carbohydrate (source of MUFA was olive oil). ii. Normal fat diet (NFD): 15% from protein, 30% from fat (10% MUFA, 10% PUFA, 10% saturated fatty acid (SFA)), and 55% from carbohydrate. iii. Diet regimen was written for each participant by a dietitian.
Zidu Xu et al	i. Aged 18 years or older ii. High risk for diabetes, as measured by the American Diabetes Association (ADA) screening tool (score of 5 or more) iii. Access to WeChat push notifications with a smartphone iv. Agreement to informed consent and further participation in the study	6-month mobile-based intervention composed of educational material sent by the WeChat subscription account named DHealthBar, WeChat applets (lightweight apps that form part of the WeChat ecosystem, which could be used independently) embedded with online questionnaires, and a check-in applet serving as an online forum with functions similar to Twitter Moments. DHealthBar was designed to educate people at high risk for T2DM about diabetes prevention and specifically focus on providing practical strategies on relevant aspects, such as (1) interventions on behavior change, (2) behavior change instructions, (3) behavior change tracking tools (ie, online questionnaires), and (4) a common space for communication and sharing.

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 4,5
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 5
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 6
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 4=6
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 6
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 6
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 6
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 6
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 6
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 6
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 6
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 6
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 6
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 6
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 6
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Page 6
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Page 6
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Page 7
Certainty	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Page 6

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PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
assessment			
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 7
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Supplementary Table
Study characteristics	17	Cite each included study and present its characteristics.	Page 7
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Page 9
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Page 8,9
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Page 9
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	NA
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Page 9
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	NA
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	NA
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	NA
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 10
	23b	Discuss any limitations of the evidence included in the review.	Page 11
	23c	Discuss any limitations of the review processes used.	Page 11
	23d	Discuss implications of the results for practice, policy, and future research.	Page 12
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 6
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 6
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	NA
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 13
Competing interests	26	Declare any competing interests of review authors.	Page 13
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Page 13

From: 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:

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Non-pharmacological interventions for the prevention of type 2 diabetes in low income and middle-income countries: a systematic review of randomized controlled trials

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Title: Non-pharmacological interventions for the prevention of type 2 diabetes in low income and middle-income countries: a systematic review of randomized controlled trials

Running title: T2DM Prevention in LMICs

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Abstract

Objective: Diabetes poses serious health threats and economic burdens to patients, especially in Low income and -Middle-Income Countries (LMICs). This systematic review searches for non-pharmacological interventions for the prevention of Type-2 Diabetes Mellitus (T2DM) among non-diabetic and prediabetes patients from LMICs.

Settings: LMICs.

Participants: Adult population aged over 18 years without having diabetes.

Primary and secondary outcomes: Primary outcome is to measure the change in the incidence of T2DM. The secondary outcome is to measure changes in HbA1c level, weight/ Body Mass Index (BMI), fasting glucose level, and 2-h glucose from baseline of the included randomized controlled trials.

Methods: This review has been conducted following the standard systematic review guidelines. A total of six electronic databases including Medline, Embase, the Cochrane Library, Web of Science, ClinicalTrials.gov, and International Clinical Trials Registry Platform were searched in February 2021 using a comprehensive search strategy.

Two sets of independent reviewers performed screening, risk of bias (ROB) assessment using the Cochrane ROB tool, and data extraction. Narrative coalescence of selected articles was demonstrated using tables. No meta-analysis was performed due to the lack of homogenous intervention strategies and study settings.

Result: A total of 5 studies were included for the review with a combined population of 1,734 from three countries. Three of the studies showed a significant reduction in T2DM incidence after the intervention of physical training and dietary modifications. Four of the studies also demonstrated a significant reduction of different secondary outcomes like weight, BMI, fasting & 2-h plasma glucose, and HbA1C. All the studies demonstrated a low risk of bias in most of the bias assessment domains with some unclear results in allocation concealments.

Conclusions: Emphasizing non-pharmacological interventions for T2DM prevention can improve health outcomes and lessen the economic burdens, which will be of paramount importance in LMICs.

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Keywords: Non-pharmacological, Prevention, T2DM

Strengths and limitations of this study

- The methodological rigor following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines is the major strength of this systematic review.
- The prime strength of this systematic review is the inclusion of Randomized Controlled Trials (RCTs) only, which helped to ensure the true effectiveness of the intervention programs
- We included articles published in English only which might have missed some potential articles published in other languages.
- Trials conducted only in India, Iran, and China fulfilled the selection criteria and were included in the review. Therefore, the interpretation might not be socially and culturally applicable to other LMICs.
- A meta-analysis could not be conducted due to the heterogeneity of the included articles.

Introduction

Diabetes mellitus is a group of metabolic disorders marked by excessive serum glucose levels caused by insufficient insulin secretion, insulin action, or both. Type 2 diabetes mellitus (T2DM) is the most prevalent form of diabetes, which accounts for 90 to 95 percent of all diabetes cases. It occurs when insulin secretion is insufficient to overcome an underlying abnormality of increased insulin resistance.[1]

Diabetes is linked to a number of adverse health outcomes. It increases the risk of cardiovascular disease and stroke significantly. In reality, most diabetic patients die of cardiovascular complications. In 2017, diabetes has risen to the 10th spot on the Institute for Health Metrics and Evaluation (IHME) global cause of death list,[2] but it directly or indirectly contributes to the other top causes of death like coronary heart disease (CHD) and stroke. Diabetic microvascular complications are the major cause of blindness, renal failure, and nontraumatic amputations.

T2DM incidence has seen a rapid global increase during the past few decades. Diabetes prevalence in the world among adults over the age of 18 increased to 8.5 percent in 2014 from 4.7 percent in 1980.[3] Diabetes affects more than 420 million individuals globally today. By 2030, this number is expected to reach 570 million, and by 2045, 700 million.[4] The burden of diabetes in terms of prevalence, incidence, Disability-Adjusted Life Years (DALYs), and death is predicted to continue to rise from 2018 to 2025.[5] The economic burden of diabetes is monumental but is usually largely overlooked. For instance, in 2019, direct and indirect medical and treatment expenses, as well as expenditures associated with diabetes-related disability and mortality exceeded $760 billion which is around 10% of total health expenditure on adults.[6, 7] This trend of economic burden is predicted to continue its upward trend.[8] Because diabetes has no cure, it is essential to focus on primary prevention via food and lifestyle changes.[1]

Uncontrolled T2DM can lead to blindness, renal failure, heart disease, and other severe complications. There is a period before diabetes is diagnosed in which blood glucose levels are elevated but not elevated enough to be labelled as diabetes. Prediabetes is the medical term for this condition.[9] It is estimated that one in every 13 adults aged 20 to 79 years has impaired glucose tolerance which amounts to 463 million people.[6] According to estimates, up to 70% of those with prediabetes progress to develop T2DM. Fortunately, advancing from prediabetes to

diabetes isn't a foregone conclusion.[10] The preventability of diabetes has been demonstrated by several randomized trials.

Early management in the prediabetes stage is beneficial to decrease diabetes development and related consequences since T2DM is a chronic illness with progressive impairment in glucose metabolism resulting in various systemic complications. Strong epidemiologic evidence indicates that diabetes is associated with lifestyle. The non-randomized Malmö study indicated that a lifestyle program for the prevention of T2DM in persons with impaired glucose tolerance is feasible.[11] Previously, randomized intervention studies showed that changes in diet and physical activity can delay or even prevent the onset of T2DM in persons with impaired glucose tolerance.[12-15] Studies in high-risk groups other than persons with impaired glucose tolerance have also been conducted. A Norwegian lifestyle intervention indicated a beneficial impact of diet and exercise on insulin sensitivity in people with several cardiovascular risk factors.[16]

A systematic literature review conducted in 2010 evaluated four cohort studies and found that the incidence of T2DM can be reduced by 28–59% by lifestyle changes.[17] A meta-analysis backs up this claim, estimating that to prevent or delay each case of diabetes, 6.4 (95% CI: 5.0–8.4) people would need to be treated through lifestyle intervention. Weight loss diets (low fat, high protein, or the Mediterranean) appear to be helpful, but every one of them has drawbacks that necessitate careful food selection. Evidence also indicates that a weight reduction maintenance strategy demands frequent exercise.[17]

More than three-quarters of the people suffering from diabetes are from low- and middle-income countries (LMICs), and diabetes prevalence is expected to rise fastest in these countries.[18] Diabetes prevalence estimates in LMICs have largely relied on self-reporting, which might have vastly understated the true prevalence of T2DM in countries lacking robust screening protocols and access to care.[19] However, In LMICs, there has been relatively little effort to adopt preventive programs and delivery approaches for T2DM.[20] Evidently, no such programs from these regions were found in a relatively fresh systematic review of 38 real-world diabetes preventive trials.[21] Given the significant differences in health systems, resources, culture, and lifestyle risk factors among LMICs, this creates a significant evidence gap. To reiterate the fact, context-specific evidence is necessary and recommended, because the burden of diabetes will proportionately decrease with the narrowing of the evidence-to-action gap. It will also lead to

lowering of death rates as well as lower healthcare expenditures.[22-24] This systematic review seeks to evaluate the effectiveness of the non-pharmacological programs for the prevention of T2DM conducted in LMICs to address that knowledge gap.

Methods

This systematic review was conducted using the Cochrane systematic review norms [25] And PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) recommendations.[25, 26] The systematic review is registered in the International Prospective Register of Systematic Reviews (Registration number: CRD42020191507). The protocol outlines the approach in-depth, including the development of the search strategy, double-screening, double-data extraction, double-quality assessment of included articles, and narrative synthesis.[27] A detailed search strategy (Supplementary Table 1) was constructed using the keywords including Exercise, "Physical activity", ''Nutritional therapy'', ''Meal plan'', "Weight loss", "Lifestyle change", "Lifestyle modification", Diabetes, "Diabetes mellitus", ''Type 2 diabetes mellitus'', T2DM, DM, LMICs, "Developing country", "Peri-urban'', urban, rural to search different electronic bibliographic database including Medline through PubMed, Embase, the Cochrane Library (Cochrane Central Register of Controlled Trials- CENTRAL), Web of Science, ClinicalTrials.gov, ICTRP, etc. The search period covered from the inception of the databases to February 2021. Non-pharmacological interventions on non-diabetic adult populations in LMICs were included in randomized control trials. Two reviewers independently screened the "title and abstract" and "full text" of the retrieved articles, and any disagreements were resolved by a third reviewer. To keep track of the screening process, reference management software "Rayyan" was used. Each study was evaluated critically for the possibility of risk of bias (ROB). A narrative synthesis of study participant characteristics and intervention categories with specific primary and secondary outcomes was demonstrated. The risk ratio (RR) of diabetes mellitus status was recorded from baseline and end line information. Mean and standard deviation of secondary outcomes (Change in weight, BMI, and fasting blood glucose level) were recorded from both the control and intervention groups.

In terms of interventions, study duration, and study settings, the included studies were too heterogeneous to be included in the meta-analysis. A narrative synthesis was performed as a substitute for a meta-analysis. We were not able to conduct a subgroup analysis or a sensitivity

analysis for the same reason. In this systematic review, we did not observe the publication bias because we were not able to perform the meta-analysis. Funnel plots are generally used to estimate the risk of publication bias. It is also recommended in different studies to avoid a test of funnel plot asymmetry or the existence of publication bias if the number of selected studies is less than 10 in a meta-analysis.[28]

Patient and public involvement

Patients or the public were not involved in the design, conduct, reporting, or dissemination plans of our research.

Results

A thorough search of the literature in the selected databases using the search strategy resulted in the retrieval of 2,737 articles. A total of 2,592 articles were finally listed for the title and abstract screening after removing 145 duplicates. A total of 25 articles were selected following employing the inclusion and exclusion criteria for the full-text review.

Figure 1: Systematic review PRISMA flow diagram

We were unable to find the full text of only one article, even after communicating with the authors. The article was published in 1984, and we excluded it from our full-text review due to unavailability. The Da Qing Impaired Glucose Tolerance (IGT) and diabetes study[12] fulfilled all the inclusion criteria, but we decided to leave the article out of our review since it used the 1985 World Health Organization (WHO) criteria to define IGT and diabetes patients. The criteria were updated in 1999. Currently, WHO[29], American Diabetes Association (ADA)[30], and Diabetes UK[31]- all use the same diagnostic criteria, and all our included studies follow this guideline for the diagnosis of diabetes and IGT. As a result, the interpretations from the Da Qing study could be potentially misleading when compared to the other selected recent studies.[32] Finally, after the full-text review, 5 articles were included for analysis. Figure 1 shows the PRISMA flow diagram of the inclusion process. Supplementary table 2 is provided containing the list of 20 articles that did not fulfill inclusion criteria and were eventually excluded, along with the reasons for exclusion.

Table 1 Attributes of studies included.

Author	Year of Publication	Sample size	Study design	Country	Age in Year	Gender	Intervention	Baseline Diabetes Status of the participants	Baseline BMI (kg/m^2)
Kavumpurathu R. Thankappan et al[33]	2018	Total- 1007 Intervention- 500 Control- 507	Cluster RCT	India	30-60	M and F	Peer-support lifestyle intervention	Non-diabetic	Not measured
Xia Dai et al[34]	2019	Total- 172 AT- 34 RT- 31 AT+RT- 37 Control- 35	RCT	China	55-75	M and F	1. Aerobic training (AT), 2. Resistance training (RT), 3. Both AT and RT	Pre-diabetic	Not measured
Arpana Gaddam et al[35]	2015	Total Sample- 140 Intervention- 74 Control- 66	Parallel RCT, single blind	India	30-70	M and F	Fenugreek powder, 5 g with 200 ml water twice a day before meals and physical activity+ diet	IFG or IGT	Control: 25.95 ± 3.04 Intervention: 26.62 ± 2.82
Shaahin Shahbazi et al[36]	2017	Total- 336 NFD- 112 HMD- 112 Control- 112	Parallel RCT	Iran	>20	M and F	1. HMD 2. NFD	Prediabetic	Presented categorically
Zidu Xu et al[37]	2020	Total-79 Intervention- 41 Control- 38	RCT	China	23-67	M and F	Mobile-based intervention+ behavioral theory	High risk of diabetes	Control: 24.7 (23.4-26.1) Intervention: 25.3 (24.7-26.2)

AT- Aerobic training, F-Female, HMD- High-monounsaturated fat diet, M- Male, NFD- Normal fat diet, RCT- Randomized Control Trial, RT- Resistance training

Five articles from three geographic regions with a combined sample of 1,734 were included for final analysis. The basic characteristics of these selected articles are given in Table 1. All the studies were recent publications, dating from 2015 to 2020. India and China both were the sites of two studies each. The Rest was conducted in Iran. Two of the five studies were randomized control trials, two were parallel randomized control trials, and the rest was cluster randomized control trial. The period of the intervention varied from six months to 36 months. Participants' age in the selected studies ranged from more than 20 years to 75 years. All of the studies had both male and female subjects as participants. The five studies used completely different intervention methods, such as peer-support lifestyle intervention,[33] Aerobic, and resistant physical training,[34] Fenugreek powder,[35] High-monounsaturated fat diet,[36] and mobile-based intervention, and behavioral theory.[37] Supplementary table 3 details the selection criteria and interventions used in each of the included articles. All the studies depicted the efficiency of the intervention in terms of the prevention of T2DM. Four of them used participants' diabetes status as the primary outcome. One study used changes in dietary behaviors and physical activity as the main outcome. The primary outcome, diabetes status, was measured by Oral Glucose Tolerance Test (OGTT) following the ADA criteria in three studies.[33-35] One study used fasting glucose level or 2-h post-glucose challenge following the ADA criteria.[36]

Table 2 shows the summary findings of the primary outcome and Table 3 and Table 4 demonstrate the secondary outcomes of the included studies. Kavumpurathu and the team evaluated the impact of peer-support lifestyle intervention to reduce the incidence of T2DM. After 12 months of intervention, the incidence of T2DM was 14.9% and 17.1% in the intervention and the control group respectively (Relative Risk: 0.88, 95% CI 0.66–1.16, p = 0.36) (Table 2). The secondary outcomes also showed improvement in the intervention groups, but it was not found to be statistically significant. Xia Dai et al examined the effect of physical training on T2DM. The intervention group had three arms, resistance training (RT), aerobic training (AT), and a combination of both (RT+AT). After 24 months of intervention, all the intervention arms showed lower cumulative incidence than the control group (22%, 26%, 21%, and 69% for the aerobic, resistance, combined, and control groups, correspondingly). The age and sex-adjusted hazard ratios were 0.26 (95% CI, 0.11-0.62) in the combined group, 0.35 (95% CI, 0.15-0.79) in the resistance group, and 0.28 (95% CI, 0.13-0.64) in the aerobic group. Among the secondary outcomes, the intervention arms showed a significant reduction in 2-h plasma

glucose level, HbA1C level (Table 3), and weight (Table 4) than the control group. The trial conducted by Arpana Gaddam et al determined the effect of Fenugreek to avert the development of T2DM in people who are prediabetic. After following the intervention and the control group for 36 months, the incidence of T2DM was found to be 18.8% and 55.7% respectively. Relative risk reduction was 0.6 ($p < 0.01$). There was also a significant reduction in fasting and 2-h plasma glucose levels.

Table 2: Summary findings of primary/ main outcome of the selected studies

Author	Duration of Intervention (months)	Primary Outcome: Diabetes Status				Risk Ratio (95% CI) *P*- value	Measurement of Primary Outcome
		Intervention		Control			
		Baseline (%)	End line (%)	Baseline (%)	End line (%)		
Kavumpurathu R. Thankappan et al[33]	12	0/500	68/456 (14.91%)	0/507	79/463 (17.06%)	0.88 (0.66– 1.16) *P*= 0.36	OGTT according to the ADA criteria
Xia Dai et al[34]	24	AT: 0/ 34 RT: 0/31 AT+RT: 0/37	Cumulative Incidence: AT: 22% RT: 26% AT+RT: 21%	0/35	Cumulative Incidence: 69%	Hazard Ratio: AT: 0.28 (0.13-0.64) RT: 0.35 (0.15-0.79) AT+RT: 0.26 (0.11- 0.62)	OGTT according to the ADA criteria
Arpana Gaddam et al[35]	36	0/ 74	Cumulative Incidence: 17/74 (22.97%)	0/ 66	Cumulative Incidence: 34/61 (55.74%)	RRR: 0.6 *P* < 0.01	OGTT
Shaahin Shahbazi[36]	24	HMD: 0/112 NFD: 0/112	HMD: 10/107 (9.35%) NFD: 14/ 106 (13.21%)	0/112	20/109 (18.35%)	HMD: 0.43 (0.1–0.9) *P* = 0.03 NFD: 0.60 (0.2–1.2) *P* = 0.1	Fasting state or 2-h post glucose challenge according to the ADA criteria
Zidu Xu et al[37]	6		-	-	-	-	Changes in dietary behaviors and physical activity

ADA- American Diabetes Association, AT- Aerobic training, HMD- High-monounsaturated fat diet, NFD- Normal fat diet, OGTT- Oral glucose tolerance test, RRR- Relative Risk Reduction, RT- Resistance training, 95% CI (95% confidence interval)

Table 3. Summary findings of secondary outcomes of the included studies (Fasting Glucose, 2 hours after plasma glucose, HbA1c)

Author	Secondary Outcomes								
	Fasting Glucose Level			2-h Plasma Glucose			HbA1c (%)		
	Intervention	Control		Intervention	Control		Intervention	Control	
	Mean (mmol/L)/ Mean Change ± SD	Mean (mmol/L)/ Mean Change ± SD	*P*-value	Mean (mmol/L)/ Mean Change ± SD	Mean (mmol/L)/ Mean Change ± SD	*P*-value	Mean/ Mean Change ± SD	Mean/ Mean Change ± SD	*P*-value
Kavumpurathu R. Thankappan et al[33]	0.225 ± 0.811	0.23 ± 0.988	0.79	0.43 ± 1.97	0.47 ± 2.11	0.63	-0.003 ± 0.43	0.056 ± 0.603	0.08
Xia Dai et al[34]	AT: 5.40 ± 0.56 RT: 5.52 ± 0.57 AT+RT: 5.08 ± 0.46	6.59 ± 0.57	-	AT: 7.48 ± 1.37 RT: 7.17 ± 1.31 AT+RT: 6.85 ± 1.78	8.26 ± 0.97	0.007	AT: 5.80 ± 0.39 RT: 5.46 ± 0.50 AT+RT: 5.52 ± 0.46	6.53 ± 0.75	<0.001
Arpana Gaddam et al[35]	Mean: 99.7 ± 11.4	Mean: 100.6 ± 11.04	<0.005	Mean: 129 ± 29.6	Mean:147.3 ± 32.6	<0.01	-	-	-
Shaahin Shahbazi[36]	HMD: −1.6 ± 8.2 NFD: −1.4 ± 7.9	4.3 ± 10.7	0.001	HMD: −3.9 ± 16.5 NFD: −0.6 ± 17.7	3.3 ± 14.8	0.005	-	-	-

AT- Aerobic training, BMI- Body Mass Index, CI- Confidence interval, HMD- High-monounsaturated fat diet, NFD- Normal fat diet, RT- Resistance training, SD- Standard deviation, NS- non-significant

Table 4: Summary findings of secondary outcomes of the included studies (Weight, BMI)

Author	Secondary Outcomes					
	Weight			BMI (kg/m²)		
	Intervention	Control		Intervention	Control	
	Mean (Kg)/ Mean Change ± SD	Mean(Kg)/ Mean Change ± SD	*P*-value	Mean/ Mean Change ± SD	Mean/ Mean Change ± SD	*P*- value
Kavumpurathu R. Thankappan et al[33]	1.22 ± 3.27	1.24± 2.91	0.95	-	-	-
Xia Dai et al[34]	AT: 57.92 ± 8.50 RT: 58.35 ± 7.73 AT+RT: 58.04 ± 7.25	65.74 ± 7.66	<0.001	-	-	-
Arpana Gaddam et al[35]	Mean: 68.79 ± 8.43	Mean: 68.34 ± 10.1	-	Mean: 26.43 ± 3.00	Mean: 25.91 ± 3.38	NS
Shaahin Shahbazi[36]	HMD: −0.1 ± 0.7 NFD: −0.09 ± 0.6	0.2 ± 2.1	0.07	-	-	-
Zidu Xu et al[37]	-	-	-	At 3 months- 24.1 (23.5-25.2) At 6 months- 23.2 (22.7-24.3)	At 3 months- 24.1 (23.3-25.6) At 6 months- 24.2 (22.8-25.6)	<0.001

AT- Aerobic training, BMI- Body Mass Index, CI- Confidence interval, HMD- High-monounsaturated fat diet, NFD- Normal fat diet, RT- Resistance training, SD- Standard deviation

* p-value indicates group-time interaction, and it denotes the significant difference among comparison groups over the intervention time period.

Shahbazi et al explored the outcomes of a fat diet without a weight-loss program on preventing or delaying the onset of T2DM in subjects with either impaired fasting glucose or impaired glucose tolerance. The intervention group had two arms, a high-monounsaturated fat diet (HMD), and a normal fat diet (NFD). After 24 months of intervention, the incidence of T2DM was 9.4%, 13.2%, and 18.4% in HMD, NFD, and control groups respectively.

Relative risk in HMD arm was 0.43 (95% CI, 0.1–0.9; P = 0.03), and in the NFD arm was 0.60; (95% CI, 0.2–1.2; P = 0.1). HMD and NFD arms were also shown to be effective in reducing the fasting and 2-h plasma glucose level significantly. Zidu Xu et al tested a Mobile-based intervention plus behavioral therapy to affect dietary behaviors and physical activity among the

population at high risk of T2DM. The control group received the same intervention through printed material. After 6 months of intervention, the intervention group showed higher reduction of BMI [3 months- 24.1 (23.5-25.2), 6 months- 23.2(22.7-24.3)] than the control group [3 months- 24.1(23.3-25.6), 6 months- 24.2(22.8-25.6)] when compared to 3-month intervention data.

The quality of the included RCTs was assessed by applying the Cochrane Risk of Bias tool. Two authors assessed the studies independently and then cross-checked the result among themselves. They warranted the judgment of the senior author to resolve some disagreement and finally came up with a combined result with consensus. Figure 2 provides a graphical demonstration of the risk of bias in the studies.

Figure 2: Risk of Bias assessment of included studies

Random sequence generation of all included studies presents a low risk of bias. Four studies[33-35, 37] used a randomization list generated by a computerized program whereas one study[36] used block randomization to minimize the selection bias. Allocation of the included studies was concealed in two studies[34, 35] through assigning a unique code and in opaque and numbered envelopes. Thus, it presents a low risk of bias for 40% of the studies whereas 60% of studies[33, 36, 37] represent an unclear risk of bias in this section. All the included studies reported their primary and secondary outcome according to their objective through which low risk of bias was reported against selective bias. One of the studies was triple blinded study[33] whereas because of the characteristics of the study, respondents were not required to be blinded in another study.[37] Two studies did not mention anything about performance bias.[34, 36] However, the study conducted by Gaddam et al.[35] portrayed a high risk of bias. Detection bias was assessed as low in four studies and unclear in one which was the opposite during assessing other biases (Low in one study and unclear among four). 80% of studies (Four) mentioned the data related to attrition or loss to follow-up. Thus, they were assessed as a low risk of bias. However, one study (20%)[34] was assessed as a high risk of bias as it conducted a per-protocol analysis having a high attrition rate. Figure 2 graphically demonstrates the ROB domains with corresponding assessment.

Discussions

The goal of this systematic review is to assess the effectiveness of non-pharmacological interventions in lowering the prevalence of T2DM in low- and middle-income countries. For this purpose, we undertook a comprehensive search strategy to screen 2,737 articles to finally select included five randomized control trials with a total population size of 1,734, spanning over the last six years, and conducted in three countries. The lack of older studies highlights the fact that non-pharmacological diabetes prevention strategies are a relatively new concept but are gaining attention lately. These trials assessed different intervention strategies like lifestyle intervention, physical training, and dietary intervention on normal or prediabetes patients. As there was no more than one study that used the same intervention strategy, no meta-analysis could be performed.

Our primary outcome was the incidence of T2DM, which was measured in the studies by assessing the OGTT or fasting glucose level and 2-h glucose challenge according to the ADA[30] or WHO[29] criteria at baseline and end-line evaluation. Among the secondary outcomes, we measured weight, BMI, fasting & 2-h glucose level, and HbA1C level to assess the effectiveness of the intervention programs.

Two studies used lifestyle intervention to reduce diabetes incidence. One used peer support, and the other study used a mobile-based app to deliver the intervention. Studies showed that lifestyle intervention lessons can lessen the probability of a person becoming diabetic.[38] The peer-support study used sittings organized by professionals and then by non-professional peer leaders to deliver the lifestyle intervention knowledge among the participants. The control group received only informational booklets. The mobile-based intervention study used mobile-app-based push notifications to deliver messages on improving dietary behaviors, physical activity, etc. The first study found a decrease in diabetes incidence after the intervention period. But the result was not statistically significant. The second study used a different primary outcome, but among the secondary outcomes, it found a significant decrease in BMI between two points of the intervention.

The efficacy of dietary modification or intervention was measured in two studies. One used Fenugreek powder for its hypothesized effect on glucose homeostasis [39-43], and the other study used an HMD and NFD regimen to elucidate the effect of dietary modification. The ADA

recommends that having the right amount of monounsaturated fat in the diet helps prevent T2DM.[44] The first study administered 5 g debittered, defatted Fenugreek powder with 200 ml water before meal two times a day for three years and found a significant decrease in relative risk for T2DM in the intervention group. They also observed a significant reduction in fasting and two-hour plasma sugar level in the intervention group. The second study contrasted an HMD and NFD group with the control group. The control group followed the United States Department of Agriculture (USDA) Food Pyramid Guide for diet. The use of a food-based US guideline in LMICs is surprising, but the study offered no explanation for this. After the intervention, the HMD section saw the most significant decrease in the incidence of diabetes compared with the NFD and non-intervention groups. The cumulative incidence also showed a marked reduction in the HFD arm.

Only one study evaluating the efficacy of supervised physical training to reduce the risk of T2DM was included in the review. This study had three intervention arms, resistance training, aerobic training, and both resistance and aerobic training. The control group was encouraged to follow normal daily activities. After two years of intervention, it demonstrated a higher cumulative incidence in the control group than in the intervention group with a significant hazard ratio. Among the arms, the combined physical training arm showed greater efficacy in diabetes risk reduction, followed by the aerobic training arm. Both the studies using Fenugreek and exercise as interventions[34, 35] were conducted among prediabetic participants and reported cumulative incidence of diabetes after the intervention period. This resulted in a much higher proportion of controls ending up as diabetic (69% and 55.74% respectively) which, however, was consistent with previous findings.[45] A joint position statement from the American College of Sports Medicine and the American Diabetes Association demonstrated the effectiveness of physical activity and physical training, especially the combination of both aerobic and resistance training.[46]

Although we left the Da Qing study out of the scope of this review, the findings from this large, randomized trial are worth mentioning nonetheless. This study recruited 577 IGT respondents, 530 of them completed the 6-year follow-up study.[12] The subjects were divided into one control and three active treatment groups (diet, exercise, diet + exercise). The cumulative incidence of diabetes was again higher in the control group (67.7%) compared to the intervention groups

(43.8%, 41.1%, and 46.0% respectively in the diet, exercise, and diet-plus-exercise group), and showed 31%, 46%, and 42% percent decreases in the risk of developing diabetes, respectively, in a proportional hazards analysis adjusted for changes in baseline BMI and fasting glucose. These findings demonstrate the similarities between the Da Qing Study and our included studies despite using older criteria accentuating the use of non-pharmacological interventions to prevent progression to diabetes.

In terms of the effectiveness, it is difficult to compare the different intervention methods due to the lack of a uniform approach of the selected studies in measuring the impact. However, exercise and dietary interventions[34-36] showed more significant results than lifestyle alone[33] in preventing the onset of T2DM, reducing body weight, and decreasing fasting glucose level. We did not find any trial comparing the effectiveness of lifestyle, exercise, and dietary interventions conducted in LMICs. Three of the selected studies[33, 35, 37] considered cultural aspects of the participants while designing the appropriate intervention. It was previously reported that culturally tailored and targeted interventions yield better results than a generalized approach to preventing diabetes.[47, 48] We also think that the distinctive difference in lifestyle, food habits, and healthcare-seeking behavior between people living in LMICs and High-Income Countries (HICs) warrant specifically-aimed interventions. This is the principal reason we explicitly chose LMICs as the place of studies to be included in this review.

We tried to broaden the reach of the review by conducting a comprehensive search in several databases but limited our searches to the English language only. There might be other studies in local languages other than English which we have missed in our search. This is one of the main limitations of our review. There were several studies conducted in other LMICs on nonpharmacological interventions for T2DM, but they were either conducted on diabetic patients, or had different primary outcomes, or on younger respondents, and so on. At the time of our search, we only found studies from Iran, China, and India that met all the inclusion criteria and were included in the systematic review. Besides, many urban settings in China are not economically different from metropolitan areas in most HICs. This fact underscores the need for further randomized controlled trials for the non-pharmacological interventions of T2DM to be conducted in LMICs. As the selected studies used different parameters and attributes to measure

the primary outcome, and they have different intervention periods, it is difficult to have an exact comparison among the studies regarding the best strategy and duration of the interventions.

The principal strength of this systematic review is the inclusion of RCTs only, which helped to ensure the true effectiveness of the intervention programs. We also followed the Cochrane guideline for systematic review stringently, which also ensured the high quality of the review. All the studies demonstrated low ROB in most of the bias assessments. There were some unclear results in allocation concealments and other biases. Four of the five studies used the same primary outcome, but all five studies used different intervention methods. The studies used a sufficient intervention period, but no crossover trials were found.

Future research should examine the efficacy of diverse non-pharmacological approaches for diabetes prevention programs. These research must adapt culturally and geographically appropriate intervention measures for LMICs to maximize their effectiveness in both clinical and community settings. Policymakers and healthcare stakeholders from LMICs should formulate health policies to mobilize resources to emphasize the non-pharmacological interventions for T2DM. Resources for diabetes prevention programs should be focused to enhance the ability to reach diverse adults and young adults at risk for type 2 diabetes.

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Authors' contributions: KMSUR conceptualized the review. AS, RD, SE, and MSI screened the articles, extracted data, and assessed the risk of bias. KMSUR resolved the conflicts in screening, data extraction, and assessment of risk of bias. AS, RD, SE, MSI and KMSUR drafted the manuscript. KMSUR reviewed, revised, and finalized the manuscript. All the authors approved the final version of the manuscript.

Conflict of interest

As for the publishing of this paper, the authors declare no conflict of interest.

Ethical approval and consent for publication

This is a systematic review incorporating published articles. No ethical approval is required. There was no involvement of any participants.

The name of the institutional Ethics Committee that approved the research: Not applicable

The approval number: Not applicable

The date of the approval: Not applicable

Data sharing statement

The datasets generated and/or analyzed during this review shall be available from the corresponding author on reasonable request.

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Supporting information:

Supplementary Table 1: Comprehensive search strategy

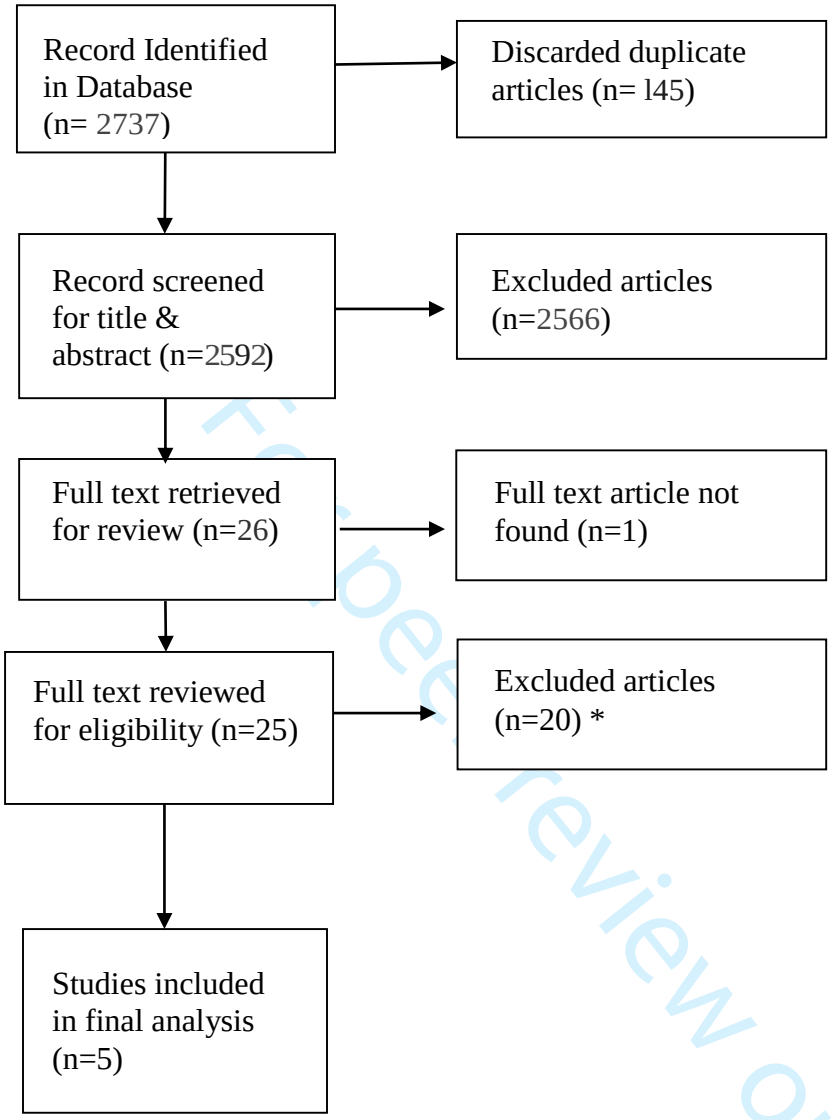
Supplementary Table 2: List of excluded articles

Supplementary Table 3. Selection criteria and interventions used by the included studies

Figure legends

Figure 1. Systematic review PRISMA flow diagram

Figure 2. Risk of Bias assessment of included studies



*Causes of exclusion: Not in LMICs= 15; Not focusing on prevention of DM = 1; Intervention provided on GDM population = 1; Not on adult = 1 Pharmacological intervention=1; Used older (WHO) criteria to define IGT and diabetes patients = 1

Figure 1: Systematic review PRISMA flow diagram

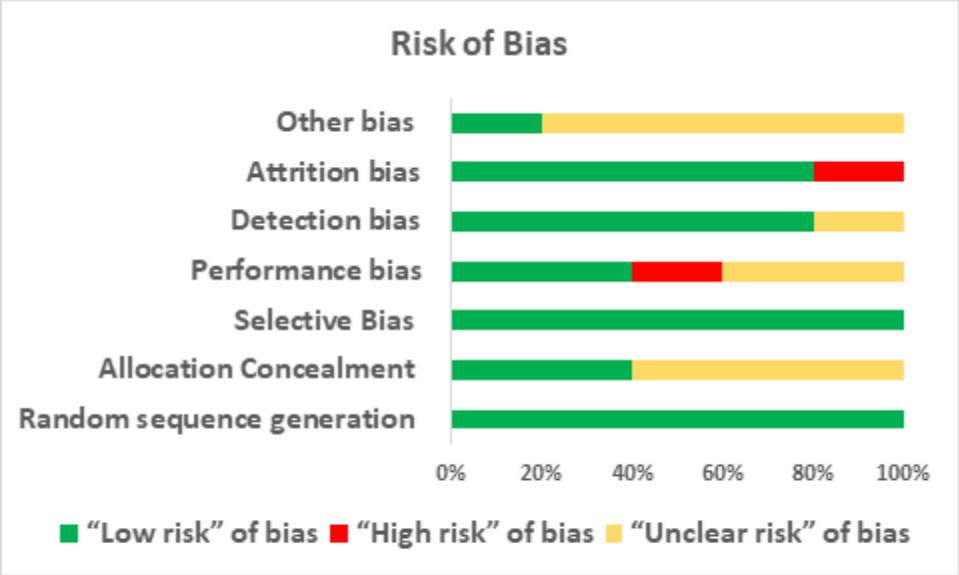


Figure 2: Risk of Bias assessment of included studies

Supplementary Table 1: Comprehensive search strategy

Sl No	Search Queries
1.	(((((LMICs) OR ("developing countries"[MeSH Terms] OR "developing countries"[All Fields] OR "developing country"[All Fields])) OR (Urban)) OR (Rural))) OR (Peri-Urban)
2.	((((((((((Exercise[MeSH Terms])))) OR (physical exercise[MeSH Terms])) OR (physical exercises[MeSH Terms])) OR (physical activities[MeSH Terms])) OR (physical activity[MeSH Terms])) OR (Exercise)) OR (Physical Exercise)) OR (Physical Activities)
3.	(((((("nutritional support"[MeSH Terms] OR "nutritional support"[All Fields]) OR "nutritional therapy"[All Fields]) OR "nutrition therapy"[MeSH Terms]) OR "nutrition therapy"[All Fields])
4.	((((Meal Plan) OR "meals"[MeSH Terms] OR "meals"[All Fields]) OR "meal"[All Fields]) AND "Plan"[All Fields])
5.	((("weight loss"[MeSH Terms] OR "weight loss/analysis"[MeSH Terms] OR "weight loss/diet therapy"[MeSH Terms] OR "weight loss/epidemiology"[MeSH Terms] OR "weight loss/metabolism"[MeSH Terms] OR "weight loss/statistics and numerical data"[MeSH Terms]) OR (weight reduction[MeSH Terms])) OR (body weight change[MeSH Terms])) OR (body weight changes[MeSH Terms])
6.	(((((((lifestyle[MeSH Terms]) OR (lifestyle risk reduction[MeSH Terms])) OR (sedentary lifestyle[MeSH Terms])) OR (life style[MeSH Terms])) OR ("life style/epidemiology"[MeSH Terms] OR "life style/analysis"[MeSH Terms])) OR (Lifestyle changes))) OR (lifestyle modifications) OR"life style"[All Fields]) OR "lifestyle"[All Fields]) OR ("Lifestyle Interventions"[All Fields])
7.	((("diabetes mellitus"[MeSH Terms] OR "diabetes mellitus, type 2"[MeSH Terms]) OR ("diabetes mellitus, type 2/analysis"[MeSH Terms] OR "diabetes mellitus, type 2/blood"[MeSH Terms] OR "diabetes mellitus, type 2/classification"[MeSH Terms] OR "diabetes mellitus, type 2/complications"[MeSH Terms] OR "diabetes mellitus, type 2/diagnosis"[MeSH Terms] OR "diabetes mellitus, type 2/diet therapy"[MeSH Terms] OR "diabetes mellitus, type 2/drug therapy"[MeSH Terms] OR "diabetes mellitus, type 2/epidemiology"[MeSH Terms] OR "diabetes mellitus, type 2/ethnology"[MeSH Terms] OR "diabetes mellitus, type 2/etiology"[MeSH Terms] OR "diabetes mellitus, type 2/history"[MeSH Terms] OR "diabetes mellitus, type 2/physiopathology"[MeSH Terms] OR "diabetes mellitus, type 2/prevention and control"[MeSH Terms] OR "diabetes mellitus, type 2/statistics and numerical data"[MeSH Terms] OR "diabetes mellitus, type 2/therapy"[MeSH Terms] OR "diabetes mellitus/analysis"[MeSH Terms])) OR ("diabetes mellitus/classification"[MeSH Terms] OR "diabetes mellitus/complications"[MeSH Terms] OR "diabetes mellitus/diagnosis"[MeSH Terms] OR "diabetes mellitus/diet therapy"[MeSH Terms] OR "diabetes mellitus/drug therapy"[MeSH Terms] OR "diabetes mellitus/epidemiology"[MeSH Terms] OR "diabetes mellitus/prevention and control"[MeSH Terms] OR "diabetic cardiomyopathies/metabolism"[MeSH Terms])) OR (("diabetes"[All Fields] AND "mellitus"[All Fields])) OR "diabetes mellitus"[All Fields]) OR "diabetic"[All Fields]) OR "diabetics"[All Fields]) OR "diabetes"[All Fields] OR "T2DM"[All Fields] OR "DM"[All Fields]

8.	"random allocation"[MeSH Terms] OR ("random"[All Fields] AND "allocation"[All Fields]) OR "random allocation"[All Fields] OR "random"[All Fields] OR "randomization"[All Fields] OR "randomized"[All Fields] OR "randomisation"[All Fields] OR "randomisations"[All Fields] OR "randomise"[All Fields] OR "randomised"[All Fields] OR "randomising"[All Fields] OR "randomizations"[All Fields] OR "randomize"[All Fields] OR "randomizes"[All Fields] OR "randomizing"[All Fields] OR "randomness"[All Fields] OR "randoms"[All Fields] OR "clinical trials as topic"[MeSH Terms] OR "clinical trials as topic"[All Fields] OR "trial"[All Fields] OR "trials"[All Fields]
9.	((clinical trials, randomized [MeSH Terms]) OR (controlled clinical trials, randomized [MeSH Terms])) OR (randomization [MeSH Terms]) OR "RCT"[All Fields] OR "RCTs"[All Fields]
10.	1 AND 2 AND 3 AND 4 AND 5 AND 6 AND 7 AND 8 AND 9
11.	Filters applied: Clinical Trial, Randomized Controlled Trial, Humans.

Supplementary Table 2: List of excluded articles

Serial no.	Author	Exclusion Criteria
1	J.A. Dunbar et al	Outside LMIC
2	Gang Hu et al	Population: GDM
3	Elroy J. Aguiar et al	Outside LMIC
4	Jessica E. Bourne et al	Outside LMIC
5	Yoshimi Fukuoka et al	Outside LMIC
6	J. Genz et al	Outside LMIC
7	Diabetes Prevention Program Research Group	Primary outcome: cost effectiveness
8	Jeffrey A. Katula et al	Outside LMIC
9	SoJung Lee et al	Outside LMIC, Population: age group 12-18years
10	Vegard Nilsen et al	Outside LMIC
11	Matthew J. O'Brien et al	Outside LMIC
12	Matthew J. O'Brien et al	Outside LMIC
13	V Ponzo et al	Outside LMIC
14	Ayman Bani Salameh et al	Population: age group 12-18y
15	Roberto P. Treviño et al	Outside LMIC, Population: 4th Grade children
16	Jaakko Tuomilehto et al	Outside LMIC
17	Katya Vargas-Ortiz et al	Control and Intervention both received Metformin
18	Peter Wein et al	Outside LMIC, Population: GDM
19	Sara Engel et al	Outside LMIC
20	Da Qing et al	Used older (WHO) criteria to define IGT and diabetes patients

GDM- Gestational Diabetes Mellitus, LMIC- Low- and middle- income- countries

Supplementary Table 3. Selection criteria and interventions used by the included studies

Author	Selection Criteria	Interventions used
Kavumpurathu R. Thankappan et al	i. No history of diabetes or other chronic illness that might affect their participation in the trial, ii. Being literate in the local language (Malayalam), iii. Not being pregnant, iv. Not taking medications known to affect glucose tolerance (glucocorticoids, antiretroviral drugs and antipsychotics) v. IDRS ≥ 60	12-month community-based peer-support program comprising 15 group sessions (12 of which were led by trained lay peer leaders) and a range of community activities to support lifestyle change.
Xia Dai et al	i. Adults aged 55 to 75 years ii. Diagnosis of prediabetes (5.6≤ fasting plasma glucose [FPG] <7.0 mmol/L and/or 7.8≤ 2- h glucose [2hPG] <11.1 mmol/L and/or 5.7%≤ haemoglobin A1c [HbA1c] <6.4%) iii. tested muscle strength more than or equal to level 4 and the ability to participate in the study timeline.	1- hour dietary class with a dietitian and a 1- hour exercise training class. 3 intervention groups selected by assigning computer-generated random numbers: i. Aerobic Training: Aerobic dancing designed by self- developed diabetes quantitative exercise prescription. ii. Resistance training: major muscle group exercises such as leg presses, leg extensions, chest presses, pull downs, rowing, and shoulder presses. iii. Combined training: 30 minutes of resistance training for three non- consecutive days per week, immediately following 30 minutes of aerobic training.

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Arpana Gaddam et al	i. Men and women aged between 30–70 years ii. Body Mass Index (BMI) ≥ 19 kg/m2, iii. Fasting plasma glucose (FPG) 100–125 mg/dl (IFG) (or) post 75 g oral glucose load, plasma glucose (oral glucose tolerance test, OGTT) 140–199 mg/dl (IGT) iv. Those who were willing to give informed consent form	Debitterized, defatted and deodorized Fenugreek fiber with vitamins, minerals and amino acids supplied by an Indian pharmaceutical industry- 5 g twice a day, was given to the intervention group along with 200 ml of water half an hour before meals and they were asked to follow the same dosage regime up to the end of study.
Shaahin Shahbazi et al	Fasting glucose level of 100–125 mg/dL (5.6–6.9 mmol/L) or a 2-h post-glucose challenge in the range of 140–199 mg/dL (7.8–11.0 mmol/L), confirmed by two tests.	i. High-monounsaturated fat diet (HMD): 15% from protein, 45% from fat (25% MUFA, 10% PUFA, 10% SFA), and 40% from carbohydrate (source of MUFA was olive oil). ii. Normal fat diet (NFD): 15% from protein, 30% from fat (10% MUFA, 10% PUFA, 10% saturated fatty acid (SFA)), and 55% from carbohydrate. iii. Diet regimen was written for each participant by a dietitian.
Zidu Xu et al	i. Aged 18 years or older ii. High risk for diabetes, as measured by the American Diabetes Association (ADA) screening tool (score of 5 or more) iii. Access to WeChat push notifications with a smartphone iv. Agreement to informed consent and further participation in the study	6-month mobile-based intervention composed of educational material sent by the WeChat subscription account named DHealthBar, WeChat applets (lightweight apps that form part of the WeChat ecosystem, which could be used independently) embedded with online questionnaires, and a check-in applet serving as an online forum with functions similar to Twitter Moments. DHealthBar was designed to educate people at high risk for T2DM about diabetes prevention and specifically focus on providing practical strategies on relevant aspects, such as (1) interventions on behavior change, (2) behavior change instructions, (3) behavior change tracking tools (ie, online questionnaires), and (4) a common space for communication and sharing.

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 4,5
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 5
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 6
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 4=6
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 6
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 6
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 6
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 6
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 6
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 6
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 6
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 6
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 6
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 6
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 6
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Page 6
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Page 6
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Page 7
Certainty	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Page 6

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
assessment			
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 7
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Supplementary Table
Study characteristics	17	Cite each included study and present its characteristics.	Page 7
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Page 9
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Page 8,9
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Page 9
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	NA
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Page 9
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	NA
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	NA
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	NA
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 10
	23b	Discuss any limitations of the evidence included in the review.	Page 11
	23c	Discuss any limitations of the review processes used.	Page 11
	23d	Discuss implications of the results for practice, policy, and future research.	Page 12
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 6
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 6
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	NA
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 13
Competing interests	26	Declare any competing interests of review authors.	Page 13
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Page 13

From: 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:

PRISMA 2020 Checklist

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