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Stephanie K. Young Date

Comparing the Cardiovascular Risk Reduction in Efficacy and Effectiveness Studies of Lifestyle Modification Interventions for Diabetes Prevention: A Systematic Review and Meta-Analysis

By

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Master of Public Health

Global Epidemiology

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Abstract

Comparing the Cardiovascular Risk Reduction in Efficacy and Effectiveness Studies of Lifestyle Modification Interventions for Diabetes Prevention: A Systematic Review and Meta-Analysis

By Stephanie K. Young

Background: Lifestyle modification are known to prevent or delay type 2 diabetes when delivered under highly controlled conditions (efficacy) and when delivered under real-world conditions (effectiveness). Although efficacy studies are expected to yield larger effects than effectiveness studies, this has not been empirically compared. In this systematic review and meta-analysis, we explored the effects of lifestyle modification (LSM) interventions on cardiovascular risk factors and explored whether effects differ between these two types of studies.

Methods: Two previous systematic reviews and meta-analysis were conducted to identify efficacy and effectiveness studies that tested the effects of LSM on diabetes risk. Studies were systematically identified through MEDLINE, Embase, Cochrane Library and Web of Science databases for efficacy studies and PubMed, Embase, Cochrane Library, and ClinicalTrials.gov for effectiveness. From these, we selected randomized control trials exploring the impact of LSM interventions. We used random effects meta-analysis to estimate pre- and post-intervention changes on systolic blood pressure (SBP), diastolic blood pressure (DBP), total cholesterol, HDL, LDL, and triglycerides for efficacy and effectiveness studies. We also used arm-based meta-analyses to compare effects between efficacy and effectiveness intervention arms.

Results: Thirty-one studies (N=7,774, mean age 51.03, 47.89% male) were included in the present meta-analysis. Efficacy LSM interventions were associated reductions in DBP (MD -2.20; 95% CI, -4.07, -0.34) and triglycerides (MD -19.51; 95% CI, -34.54, -4.48) compared to controls. Effectiveness interventions were not associated with significant changes for any outcomes compared to controls. When comparing the effects of efficacy and effectiveness interventions, efficacy interventions were associated with greater reductions in SBP (MD -4.67; 95% CI, -7.22, -2.14), DBP (MD -2.67; 95% CI, -3.76, -1.58), and triglycerides (MD -20.17; 95% CI, -29.31, -11.04).

Conclusions: Although both efficacy and effectiveness studies show improvement in cardiovascular outcomes in populations at risk for type 2 diabetes, efficacy studies are significantly more beneficial for certain outcomes, namely DBP and triglycerides. Future studies should aim to identify methods and tools that can be used to mitigate the discrepancy between efficacy and effectiveness interventions. In doing so, real-world interventions can achieve similar results to those achieved in clinical trials and other efficacy-based studies.

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INTRODUCTION

The Global Burden of Type 2 Diabetes

Diabetes is a burdensome and prevalent disease that is increasing at alarming rates worldwide. In 1980, 108 million people, accounting for 4.7% of the world's adult population, were living with diabetes. By 2014, thirty-four years later, 314 million more people, 8.5% of the world's population, were living with the burdensome disease (1). In 2016, an estimated 1.6 million deaths were caused directly by diabetes, and an additional 2.2 million were caused indirectly by high blood glucose (2). Moreover, diabetes is the leading cause of end-stage renal failure, adult-onset blindness, and nontraumatic amputations, and contributes to cardiovascular morbidity and mortality (3). In addition to public health burden, diabetes poses substantial financial burdens at both the individual and population-level. The estimated cost of diabetes in 2015 was US$1.31 trillion, accounting for 1.8% of the global gross domestic product (4). A study of US healthcare spending found that diabetes was more costly than any other condition (5). Individuals with diagnosed diabetes spend 2.3 times more on healthcare costs than they would in the absence of diabetes, with an average cost of $9,601 in diabetes-related medical expenditures each year (6). The present burden and increasing incidence of diabetes points to the crucial, urgent need to combat this serious pandemic. This thesis focuses on type 2 diabetes (referred to as "diabetes" from here), which accounts for 95% of all diabetes cases worldwide (7).

Although diabetes has been increasing worldwide in recent decades, Asia is the epicenter of this global epidemic, with China and India bearing the greatest burden. In 2015, the US was listed as the country with the third-larger number of people with diabetes. Notably, in China and India, diabetes is associated with lower BMI and younger age of onset

than in Western populations. Pacific countries have a high prevalence of diabetes, affecting over 30% of the population in American Samoa and 25% in Polynesia and Micronesia. In the Middle East, Saudi Arabia is the country with the highest diabetes prevalence affecting 25.4% of adults. In Latin American countries, diabetes was ranked as one of the leading causes of morbidity and mortality. Given that there are variations in diabetes diagnostic criteria, and lack of data in some developing countries, these estimates, while alarming, likely underrepresent the true burden of diabetes (8). The leading cause of morbidity and mortality for type 2 diabetes patients is cardiovascular complications. Compared with individuals without diabetes, diabetes patients are disproportionately affected by cardiovascular disease and associated morbidity compared to those without diabetes (9). Moreover, kidney complications are highly prevalent in Asian patients with diabetes (8).

Diabetes Prevention Interventions

Prediabetes is state of hyperglycemia in which glucose are lower than diabetes thresholds, but higher than normal levels. Prediabetes is characterized by impaired fasting glucose (IFG) and impaired glucose tolerance (IGT). IFG is diagnosed when fasting plasma glucose (FPG) levels are 100-125 mg/dL, and IGT is diagnosed when 2-hour plasma glucose levels are 140-199 mg/dL after an oral glucose tolerance test (OGTT). Additionally, glycated hemoglobin (HbA1c) indicates chronic hyperglycemia, and values 5.7-6.4% indicate prediabetes (10).

Individuals with prediabetes have a 50 percent risk of developing diabetes in the next 5 to 10 years, unless lifestyle changes are made (11). Individuals with IFG progress to diabetes when they reach FPG ≥126 mg/dL, and those with IGT when they reach 2-hour plasma glucose after an OGTT ≥200 mg/dL, or an HbA1c value ≥6.5 (10, 12). A random

plasma glucose ≥200 mg/dL can also be used to detect diabetes in certain patients with hyperglycemia symptoms. Of the available diagnostic criteria, HbA1c is considered a more convenient and stable method than IFG and OGTT. However, HbA1c is more costly and not available in some settings (13).

Overweight and obesity are strong drivers of diabetes risk in high BMI populations (Nguyen, Nguyen, Lane, & Wang, 2011), thus, physical activity and diet modification interventions have been the focus of many national and global diabetes prevention efforts (14, 15, 16, 17). For example, the US Diabetes Prevention Program (DPP) was a randomized controlled trial (RCT) that examined whether lifestyle modification, defined as 150 minutes of moderate-to-vigorous intensity physical activity per week per week and weight loss of 7%, prevented type 2 diabetes to a greater extent than taking metformin or receiving no intervention. After 3 years, the DPP showed that participants in the lifestyle modification arm lowered their risk of developing diabetes by 58% compared to the control arm, while the metformin arm lowered their risk by 31% compared to the control arm. The DPP proved to be effective for all racial and ethnic groups at reducing diabetes risk for both men and women. The DPP study provided convincing evidence on the impact of lifestyle modification for the prevention of type 2 diabetes and has been used as a model for subsequent diabetes prevention programs (14).

Similar RCT's have been conducted worldwide. In a study conducted by Li et al. in Da Qing city, China, adults with IGT took place in a 6-year lifestyle intervention that modified of diet, exercise, or both diet and exercise. Patients were followed-up with 20 years after the intervention to assess the long-term effect of the interventions. The lifestyle intervention arms were found to have a 51% lower diabetes incidence rate during the active intervention and a 43% lower incidence over the 20-year period compared to the control

arm. Lindstrom et al. conducted a similar study in Finland, examining the impact of diet and exercise on glucose and lipid metabolism in subjects who were overweight or with impaired glucose tolerance. Follow-up took place after the 1-year intervention, and then 2 years later after the washout period. The intensive lifestyle intervention improved diet, physical activity, blood glucose, and lipid concentrations, and showed a significant reduction in diabetes incidence. In another similar study conducted by Ramachandran et al., Asian Indians with impaired glucose tolerance received lifestyle modification and metformin to prevent type 2 diabetes, with a particular focus on how Asian Indians' progression to diabetes differs from other populations. It was determined that progression from IGT to diabetes was high in Asian Indians, but both lifestyle modification and metformin significantly reduced the incidence of diabetes in Asian Indians with IGT. As evidenced by these large-scale studies and other similar studies, lifestyle modification has proved to be an effective intervention for the prevention of diabetes, and improvement of related risk factors, such as weight, lipids, and blood glucose in a variety of populations worldwide.

Efficacy and Effectiveness of Diabetes Prevention Interventions

In health intervention research, there are two types of evidence, which are determined by the study setting: efficacy and effectiveness. Efficacy refers to the benefits and harms of an intervention when tested under optimal conditions, while effectiveness refers to the benefits and harms of an intervention when tested under real-world conditions (18). Efficacy studies are concerned with internal validity, that is, evidence that the obtained results are free of error. As such, they are typically resource-intensive, highly controlled, have a highly-selected and homogeneous populations, and often select highly-experienced providers to deliver the intervention in clinical settings. In contrast, effectiveness studies are

concerned with external validity, which refers to the extent to which results are generalizable to other populations and are thus conducted among heterogeneous populations, using less stringent inclusion criteria and a wide range of intervention delivery personnel. Efficacy studies are often valued for providing unbiased intervention effects (i.e. less prone to error), while effectiveness studies are often considered more relevant for real-world decision-making (19).

Two previous systematic reviews and meta-analyses laid the groundwork for the present thesis; these examined the efficacy and effectiveness of lifestyle modification diabetes prevention interventions, respectively. Systematic reviews involve a detailed, comprehensive plan and search strategy developed a priori to identify studies relevant to a specific research question. The plan and search strategy are developed to identify, assess, and synthesize all studies pertaining to a given research question, and they are determined a priori to reduce the risk of bias. A meta-analysis is an additional component to a systematic review, with the purpose of employing statistical techniques to synthesize the data from the identified studies. In a meta-analysis, data from several studies are collected in a standardized format (i.e. converted to the same units) and synthesized into summary effect sizes or other quantitative estimates. Effect sizes measure the strength of a relationship between two variables, and thus estimate the magnitude of an intervention's effect. For a combined systematic review and meta-analysis, there are 8 key stages: 1) formulate the research question; 2) define inclusion and exclusion criteria; 3) develop search strategy and locate studies; 4) select studies; 5) extract data; 6) assess data quality; 7) analyze and interpret results; and 8) disseminate findings (20). Systematic reviews and meta-analyses are considered to provide the strongest evidence around intervention or treatment effects and are powerful tools to inform health practices, programs, and policies.

The first systematic review and meta-analysis estimated the efficacy of lifestyle modification for preventing diabetes in adults with prediabetes. In this meta-analysis of 19 RCTs, lifestyle modification was associated with a relative risk reduction of 39% at the end of the active intervention, and a 28% reduction at the end of the washout or follow-up period. The effect of medications was also analyzed, showing a relative risk reduction of 36% at the end of the active intervention, but no reduction at the end of the washout or follow-up period (21). The second systematic review and meta-analysis estimated the effectiveness of lifestyle modification interventions for preventing diabetes in populations with prediabetes or at high-risk for diabetes. In this study, there were 25 single-group pre-post studies, 22 RCTs, and 16 non-randomized controlled studies that were analyzed using a network meta-analysis method. Lifestyle modification was found to be associated with a 29% relative risk reduction at the end of the intervention period (22). In line with previous conclusions (23), these results show efficacy meta-analysis yield larger effect sizes than effectiveness studies, but this notion has not been empirically tested in a combined analysis.

Few meta-analyses have estimated the effects of lifestyle modification on cardiovascular outcomes. In a meta-analysis that examined lifestyle modification on cardiovascular (CVD) outcomes in patients with type 2 diabetes, there were favorable changes in body mass index (BMI), HbA1c, systolic blood pressure (SBP), and diastolic blood pressure (DBP) in the intervention arm compared to the control. However, there were no favorable changes in high-density lipoprotein (HDL) cholesterol and low-density lipoprotein (LDL) cholesterol (24). Another meta-analysis, which compared lifestyle modification and drug interventions for the prevention of diabetes and CVD, found that neither lifestyle modification nor drug interventions reduced CVD death. However, authors noted that a lack of statistical power may have limited their results, as a majority of the

studies they included were not intended to measure CVD outcomes (25). A similar meta-analysis yielded contrary results to Hu's meta-analysis, concluding that lifestyle modification programs were associated with reduced all-cause mortality and cardiac mortality, among other CVD-related improvements (26). Another meta-analysis specifically examined the effect of the Mediterranean-style diet on glucose and lipid outcomes in patients with type 2 diabetes. Compared to control diets, the diet led to greater benefits for total cholesterol, triglycerides, HDL, SBP, DBP, HbA1c, FPG, fasting insulin, BMI, and body weight (27). Moreover, another meta-analysis that studied the impact of lifestyle modification on metabolic syndrome found that the intervention arms experienced significant reductions in SBP, DBP, and triglycerides, among other beneficial outcomes, compared to the control. However, there was not a significant reduction in HDL. The existing meta-analyses support that lifestyle modification improves CVD risk factors and may reduce CVD mortality.

The present meta-analysis aims to further explore the impact of lifestyle modification using a novel approach: estimating the efficacy and effectiveness of lifestyle modification diabetes prevention interventions on cardiovascular risk factor modification. Additionally, the meta-analysis will compare effect sizes between efficacy and effectiveness studies. This analysis can help illuminate gaps in intervention effects and inform decisions around type 2 diabetes prevention strategies.

METHODS

As mentioned, two systematic reviews and meta-analyses were conducted exploring the impact of lifestyle modification interventions on diabetes risk: one was focused on the efficacy of such interventions (21) and the other focused on their effectiveness (22). The present meta-analysis explores the effect of lifestyle modification interventions on

cardiovascular risk factors, and also aims to determine whether these effects differ between efficacy (i.e. tested under ideal conditions) and effectiveness studies (i.e. tested under real world conditions). This review adheres to PRISMA reporting guidelines for systematic reviews and meta-analyses (28). Below, we briefly describe the methods used for each systematic review and meta-analyses, which are summarized in Table 1, and then describe the methods employed for the present thesis.

Efficacy Systematic Review and Meta-Analysis

MEDLINE, Embase, Cochrane Library, and Web of Science were searched for eligible articles published and indexed between January 1, 1990 and January 1, 2015. Combinations of Medical Subject Headings and search terms, including prediabetes, primary prevention, and risk reduction were used. The search was not restricted based on language, and non-English articles were translated.

Studies eligible for inclusion were RCTs testing the efficacy of diabetes prevention interventions lasting at least 6 months in adults with prediabetes that reported between-treatment group difference in diabetes incidence rates. Studies ineligible for inclusion were those involving participants with type 1 or 2 diabetes, gestational diabetes, metabolic syndrome (where prediabetes was not confirmed), and participants younger than 18 years. Studies evaluating alternative therapies and bariatric surgeries, due to the impact of additional factors associated with these treatments, were also excluded.

From the selected studies, the number of persons who developed diabetes at the end of the intervention period was extracted or calculated. Mean changes from baseline to end of intervention in body weight, fasting blood glucose, 2-hour post-challenge glucose, hemoglobin A1c, systolic and diastolic blood pressure. LDL and HDL cholesterol, total

cholesterol, and triglycerides were also extracted. Participant characteristics (e.g. age and sex) and study characteristics (e.g. country, design) were extracted. Data were obtained using standardized extraction templates.

The Jadad tool (29) was employed to assess the quality of the included studies. The first indicator in this tool was blinding: whether the study blinded participants or healthcare professionals (1 point), both (2 points), or neither (0 points). The second indicator was attrition: whether the study reported an attrition rate of less than 20% (2 points), greater than 20% (1 point), or differential attrition between groups (0 points). The third indicator was whether statistical methods were employed to minimize the impact of attrition: if intent to treat analysis (2-points) or per protocol (1 point) were used, or none were reported (0 points). Because all of the studies were RCTs, the random allocation indicator was not a suitable indicator and was replaced by a fourth indicator: the use of CONSORT guidelines (30) for appropriate RCT reporting (2 points), no guidelines were used but reporting was clear (1 point), or reporting was unclear (0 points). The indicator scores were summed to determine composite quality scores for each study. Studies with a composite score of 0-3 points were classified as "low quality;" 4-6 as "medium quality;" and 7-8 as "high quality." Of note, the Jadad tool's indicators differ from those to assess quality for effectiveness meta-analysis, which is a possible limitation since the quality scores are not comparable.

The goal of this meta-analysis was to estimate the efficacy of lifestyle modification interventions for preventing diabetes. Random effects meta-analysis models were used to estimate the aggregate relative risk for diabetes between intervention and control participants. Heterogeneity across studies was explored by computing I^2, where I^2>75% indicated significant heterogeneity. Meta-regressions were used to understand the contribution of participant demographics and weight change on intervention effect

heterogeneity (31). Publication bias was assessed using Egger's test and by visual examination of funnel plots.

Effectiveness Systematic Review and Meta-Analysis

PubMed, Embase, Cochrane Library, and ClinicalTrials.gov electronic databases were searched for articles published between January 1990 and April 2015 reporting on the effectiveness of real-world lifestyle modification interventions to prevent diabetes. A combination of Medical Subject Headings and terms related to diabetes prevention, lifestyle modification, and translation research were used.

Effectiveness or translation intervention studies (i.e. implemented under real world conditions or translations of proven interventions) of any study design were included. To be eligible, the study had to test an lifestyle modification strategy (defined as any physical activity and/or diet to prevent diabetes), be directed at objectively high-risk populations (e.g. African Americans), and report type 2 diabetes incidence rates, weight, or glucose outcomes (fasting blood glucose, 2-hour post-challenge glucose, or hemoglobin A_{1C}) before and after the lifestyle modification intervention. Studies that were ineligible for inclusion were those with a sample prevalence of gestational diabetes mellitus >20%, metabolic syndrome, participants under 18 years of age, type 1 diabetes, or efficacy studies (i.e., delivered under highly controlled conditions).

The number of participants who developed diabetes by the end of the study period and crude incidence rates were extracted in order to study the outcomes of interest: relative risk, and likelihood, of developing diabetes. Mean changes from baseline to end of intervention in body weight, fasting blood glucose, 2-hour post-challenge glucose, hemoglobin A1c, systolic and diastolic blood pressure, LDL and HDL cholesterol, total

cholesterol, and triglycerides were extracted. Participant-level characteristics (e.g., age, ethnicity) and program-level characteristics (e.g., duration of intervention) were also extracted. Data was extracted using a standardized extraction form designed for this study.

Study quality was assessed using a set of quality indicators that are relevant to translation studies and which have been previously used in meta-analyses of translation studies (32, 33). As previously mentioned, this set of quality indicators differs from the Jaded tool indicators that were used for the efficacy meta-analysis, which is a possible limitation since the quality scores are not comparable. The first indicator used to assess quality was whether the risk of diabetes was determined using blood glucose (2 points) or self-reported risk or anthropometric measurements (1 point). The second indicator was attrition: whether the study reported an attrition rate of less than 20% (2 points), 20–40% (1 point), or differential between groups (0 points). The third indicator was whether intent-to-treat analysis was used to minimize the impact of attrition (2 points) or if per-protocol analysis was used (1 point) was used. The fourth quality indicator was whether the study described the intervention sufficiently enough to allow transferability to other settings. This indicator was measured by the following (1 point each): description of the intervention program, costs to implement the program, qualification of those implementing the intervention, and the program's acceptability among providers and/or participants. The indicator scores were summed to determine composite quality scores for each study. Using a scale of 1–10, each study was categorized as low (0–5 points), medium (6–7 points) or high (8–10 points) quality.

The goal of this meta-analysis was to estimate the effectiveness of lifestyle modification interventions for preventing diabetes. Random effects meta-analysis models were used to estimate the aggregate relative risk for diabetes between intervention and

control participants. Random effects meta-analysis models were also used to estimate the pooled mean difference in weight and glucose outcomes between control and intervention arms. Heterogeneity across studies was estimated by computing I^2, where I^2 values greater than 75% indicated significant heterogeneity, and by visual examination of forest plots. Meta-regressions were employed to determine what factors led to heterogeneity in treatment effects, examining the impact of both participant and study-level characteristics. Publication bias was assessed using Egger's tests and by visual examination of funnel plots.

Table 1. Comparison of Methods in Efficacy and Effectiveness Systematic Reviews and Meta-Analyses

Method	Efficacy Systematic Review and Meta-Analysis		Effectiveness Systematic Review and Meta-Analysis	
Databases Searched	MEDLINE, Embase, Cochrane Library, Web of Science		PubMed, Embase, Cochrane Library, ClinicalTrials.gov electronic databases	
Publication Dates	Articles Published and Indexed January 1, 1990–January 1, 2015		Articles published January 1990–April 2015	
Search Terms and Dates	Combinations of Medical Subject Headings and search terms, such as *prediabetes*, *primary prevention*, and *risk reduction.* Initial search conducted January 14, 2014, and updated search performed February 20, 2015		Combination of search and Medical Subject Headings terms related to diabetes prevention, lifestyle modification, and translation research	
Inclusion criteria for Study Selection (PICOS)	Population	Adults (at least 18 years old) with prediabetes, defined by either impaired glucose tolerance (IGT), impaired fasting glucose (IFG), or both	Population	Populations at high-risk for diabetes by objective measures
	Intervention	Efficacy of diabetes interventions lasting at least 6 months	Intervention	Effectiveness or translation studies (implemented under real-world conditions) testing lifestyle modification strategy
	Comparator	Between-group differences	Comparator	Diabetes outcomes before and after intervention
	Outcome(s)	Diabetes incidence rates at the end of active intervention	Outcome(s)	Relative risk and likelihood of developing diabetes, measured by type 2 diabetes incidence rates, weight, or glucose outcomes
	Study design	Randomized control trials	Study design	Any study design
Quality Metrics	- Blinding: whether the study blinded participants or health care professionals (1 point), both (2 points), or neither (0 points) - Attrition: whether an attrition rate of less than 20% (2 points), over 20% (1 point), or differential between groups (0 points) - The use of statistical methods to assess the impact of attrition: intent-to-treat analysis (2 points), per protocol (1 point), or if none were reported (0 points) - The use of CONSORT guidelines for appropriate RCT reporting (2 points) no guidelines were used but reporting was clear (1 point), or reporting was unclear (0 points)		- Diabetes Risk Assessment: whether diabetes risk was defined using blood glucose testing (2 points) or self-reported risk factors or anthropometric measurements (1 point) - Attrition: whether reported study attrition was 20% (2 points), 20–40% (1 point), or different between study arms (0 points) - Whether intent-to- treat analysis was used to minimize the impact of attrition (2 points) per- protocol analysis (1 point) - Whether the study described the intervention sufficiently enough to allow transferability to other settings. (1 point each): description of the intervention; costs and resources to deliver the program; the qualification of those implementing the intervention; and the acceptability of the program among participants and/or providers	

The Present Meta-Analysis

The present analysis aims to estimate the effect of lifestyle modification interventions on CVD risk factors that were not explored in the previous meta-analyses: systolic and diastolic blood pressure, LDL and HDL cholesterol, total cholesterol, triglycerides, and body weight. It also aims to compare whether effects on these outcomes differ between efficacy and effectiveness studies.

Study Selection

From the studies included in the two previously published meta-analyses, we selected only RCTs which tested a lifestyle modification intervention (i.e. change in diet, exercise, or both). Additionally, we only included studies that reported at least one of the following values: pre- or post-intervention SBP, DBP, total cholesterol, HDL cholesterol, LDL, cholesterol, triglycerides, or weight.

Data Extraction

For the present meta-analysis, pre- and post-intervention mean values and standard deviations were extracted for: SBP (mmHg), DBP (mmHg), total cholesterol (mg/dL), HDL cholesterol (mg/dL), LDL cholesterol (mg/dL), triglycerides, and weight (kg). Additionally, change between pre-and post-intervention means and the standard deviation of this change were either extracted or calculated. Participant characteristics extracted include mean age (years), percent of male participants, and participant race. Study-level characteristics extracted include sample size at baseline, sample size included in analysis, type of lifestyle modification intervention (e.g. diet, exercise, diet and exercise, individual-level counseling,

group-level counseling), duration of intervention (years), quality category, and country of study. When data was not reported but needed for the analysis, we calculated the needed values or excluded the study in the meta-analysis for the respective outcome.

Statistical Analysis

We used random effects meta-analysis models to account for heterogeneity between studies. For the first meta-analysis we conducted, we estimated the pooled mean difference in cardiovascular risk factors between control and intervention arms from pre- and post-intervention for both efficacy and effectiveness studies separately. In other words, we compared efficacy intervention arms to efficacy control arms, and compared effectiveness intervention arms to effectiveness control arms, in order to determine the effect sizes for each of these study types individually. For the second meta-analysis, we used a frequentist arm-based random effects meta-analysis approach to estimate the pooled mean difference in cardiovascular risk factors between efficacy intervention arms and effectiveness intervention arms. For this meta-analysis, we excluded control arms and treated effectiveness as the reference group to compare against efficacy interventions arms.

We estimated effect heterogeneity across studies using I^2, where a value greater than 75% indicated significant heterogeneity. We used univariate and multivariate meta-regressions to explore the influence of participant and study-level characteristics (mean age, percent male, mean baseline value for the respective outcome, and duration of intervention) on effect heterogeneity for both the analyses that we conducted, and also to determine if these factors explained the difference between efficacy and effectiveness summary estimates.

Publication bias was assessed using Egger's test and by visual examination of funnel plots. The metafor package in R (34) was used to fit the models described for the present

study. We determined statistical significance by examining 95% confidence intervals; confidence intervals not including 0 for pooled mean differences were deemed statistically significant.

RESULTS

Study Characteristics

Of the articles included in the previously published efficacy and effectiveness systematic reviews (efficacy, N = 43; effectiveness, N=63), 32 were included in this meta-analysis. Seventy-four were excluded because they were not RCTs or did not include lifestyle modification as an intervention (Figure 1). Participant and intervention characteristics by study type across the 32 included studies are presented in Table 2. Of the included studies, 27 (84%) employed individualized counseling, group education, or both as interventions. Individualized counseling was the most common form of intervention employed in efficacy studies (53%), while group education was the most common form of intervention employed in effectiveness studies. The remaining studies employed text message-based lifestyle modification, and dietary plan and/or exercise plan. Study follow-up length ranged from 0.5 to 4 years (mean [SD], 2.51 [1.15] years).

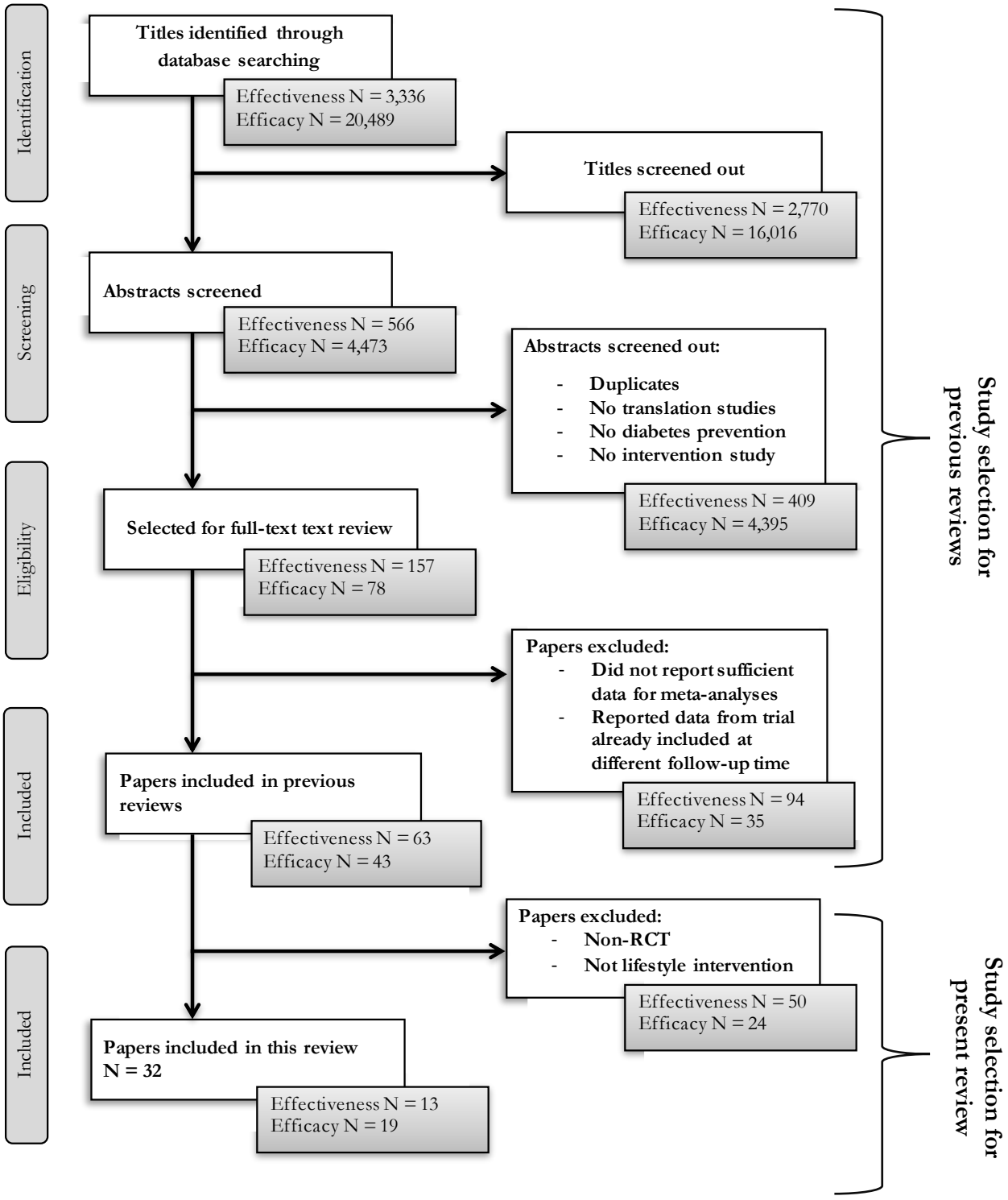

Figure 1. PRISMA Study Identification Flow Diagram

The total number of participants across the 32 studies was 7,774 at baseline (mean [SD] age, 51.0 [7.0] years; 47.9% men). In the efficacy studies, there were 6,086 participants at baseline: 2,930 in the intervention arm and 3,150 in the control. In the effectiveness studies, there were 1,688 participants at baseline: 868 in the intervention arm and 820 in the control.

Thirty-four percent of all studies included in our analysis were conducted in the US, 16% in Japan, 13% in China, 9% in the UK, 6% in Australia, and 3% (1 study each) were conducted in Canada, Finland, India, Israel, Korea, Netherlands, and Norway. Baseline CVD measures were less favorable for the efficacy studies, with higher mean values for SBP, DBP, total cholesterol, LDL, and triglycerides, lower HDL effectiveness studies. The percent male reported for the efficacy studies was 50.8%, compared to 37.5% for the effectiveness studies, and the mean age was slightly higher for efficacy studies (mean [SD], 51.2 [4.4] years) than the effectiveness studies (mean [SD], 50.6 [9.6] years).

Table 2. Characteristics of Participants and Studies Included in Meta-Analyses.

Baseline participant-level characteristics (N=7,774)*	**Efficacy (n=6,086) Mean (SD) or %**	**Effectiveness (n=1,688) Mean (SD) or %**
Age (years)	51.2 (4.4)	50.6 (9.6)
Male	50.8%	37.5%
Systolic Blood Pressure (mmHg)	130.7 (6.3)	126.7 (7.5)
Diastolic blood pressure (mmHg)	80.2 (5.7)	76.8 (5.2)
Total cholesterol (mg/dL)	208.4 (11.9)	189.8 (23.4)
HDL cholesterol (mg/dL)	49.9 (4.3)	50.8 (4.6)
LDL cholesterol (mg/dL)	125.5 (10.1)	111.9 (11.4)
Triglyercides	144.9 (22.4)	141.1 (19.5)
Study-level characteristics (N=32)	**n=19 studies Number (%)**	**n=13 studies Number (%)**
Country of Study		
United States	2 (11%)	9 (69%)
Japan	4 (21%)	1 (8%)
China	4 (21%)	0 (0%)
UK	2 (11%)	1 (8%)
Australia	1 (5%)	1 (8%)
Canada, Finland, India, Israel**, Korea, Netherlands, Norway (one each)	6 (32%)	1 (8%)
Race of Participants		
Asian	11 (58%)	4 (31%)
White	3 (16%)	4 (31%)
Hispanic	0 (0%)	2 (17%)
Multiple	2 (11%)	0 (0%)
Indigenous	0 (0%)	1 (8%)
Not Reported	3 (16%)	2 (13%)
Intervention strategy		
Individualized counseling and group education	1 (5%)	1 (8%)
Individualized counseling	10 (53%)	3 (23%)
Group education	3 (16%)	9 (69%)
Text messages for lifestyle modification	1 (5%)	0 (0%)
Dietary and exercise plan	2 (11%)	0 (0%)
Dietary plan/daily meal replacement	2 (11%)	0 (0%)

*Baseline participant-level characteristics calculated using weighted averages by the number of participants reported at baseline for each study

** Effectiveness study; all other countries listed were the site of efficacy studies

Note: HDL: high-density lipoprotein; LDL: low-density lipoprotein

Effect of Lifestyle Modification Interventions on Cardiovascular Measures

Efficacy estimates are summarized in Table 3. The estimates represent the difference in pooled effect sizes between the intervention and control arms. Greater reductions (i.e. lower values) indicate more beneficial effects for all outcomes except HDL, the only outcome for which higher values are more beneficial. During the active intervention period, efficacy interventions arms achieved greater improvements in some cardiovascular outcomes compared to the control arms, namely SBP, DBP, and triglycerides (difference between arms in pooled effect size [95% CI]): SBP (-4.67 [-7.22, -2.14] mmHg), DBP (-2.67 [-3.76, -1.58] mmHg); and triglycerides (-20.17 [-29.31, -11.03] mg/dL). There were no significant differences between intervention and control arms for total cholesterol, HDL, and LDL. Effects were heterogeneous for some outcomes, with I^2 ranging from 30.7% for DBP, to 87.5% for LDL.

Table 3. Comparison of Intervention to Control Arms in Efficacy and Effectiveness Studies

	Efficacy (N=19)		Effectiveness (N=13)	
Outcome	**Pooled MD (95% CI)**	**N (I^2)**	**Pooled MD (95% CI)**	**N (I^2)**
SBP (mmHg)	-4.67 (-7.22, -2.14)*	9 (65.6%)	-0.53 (-3.58, 2.52)	10 (78.9%)
DBP (mmHg)	-2.67 (-3.76, -1.58)*	9 (30.7%)	-0.54 (-1.16, 0.09)	7 (0%)
Total Cholesterol (mg/dL)	-3.48 (-9.17, 2.21)	8 (86.5%)	0.16 (-6.02, 5.70)	8 (71.2%)
HDL (mg/dL)	1.28 (0.14, 2.41)	8 (36.2%)	1.19 (-0.98, 3.36)	8 (85.1%)
LDL (mg/dL)	-0.06 (-8.27, 8.16)	8 (87.5%)	-2.17 (-6.43, 2.08)	5 (0%)
Triglycerides (mg/dL)	-20.17 (-29.31, -11.03)*	5 (52.3%)	-5.45 (-15.42, 5.52)	4 (0%)

*Statistically significant result
N: number of study arms included in analysis
MD: mean difference
Note: SBP: systolic blood pressure; DBP: diastolic blood pressure; HDL: high-density lipoprotein; LDL: low-density lipoprotein

Effectiveness estimates are summarized in Table 3. The estimates represent the difference in pooled effect sizes between the intervention and control arms. During the active intervention period, effectiveness interventions arms achieved greater improvements

than the control arms in SBP (-0.53 [-3.58, 2.52] mmHg), DBP (-0.54 [-1.16, 0.09]) mmHg), HDL (1.19 [-0.98, 3.36] mg/dL, LDL (-2.17 [-6.43, 2.09] mg/dL) and triglycerides (-5.45 [-15.42, 5.52] mg/dL). There we no effects on total cholesterol (0.16 [-6.02, 5.70] mg/dL). Effects in these outcomes were heterogeneous for HDL (85.1%) only.

Comparison of Efficacy Intervention Arms to Effectiveness Intervention Arms

We compared the effects of efficacy and effectiveness intervention arms to explore differences in effect sizes between the two study types. The control arms were excluded from this analysis and the the effectiveness intervention arms were treated as the reference arms. The results of this comparative analysis are summarized in Table 4. Overall, efficacy intervention arms achieved greater improvements in cardiovascular outcomes compared to effectiveness intervention arms, although results were not statistically significant for all outcomes. Compared to effectiveness, efficacy intervention arms were associated with significantly larger decreases in DBP (-2.20 [-4.07, -0.34] mmHg) and triglycerides (-19.51 [-34.54, -4.48] mg/dL). Efficacy intervention arms were associated with larger decreases in SBP (-1.34 [-4.84, 2.15]); total cholesterol (-1.10 [-11.34, 9.13]); and HDL cholesterol (-0.44 [-2.47, 1.60]) than effectiveness intervention arms. Of note, higher values of HDL cholesterol are more favorable, so the effectiveness intervention arms achieved better results than efficacy intervention arms for HDL. Additionally, efficacy intervention arms were associated with increases in LDL cholesterol (2.18 [-3.03, 7.38]) and weight (0.75 [-1.0, 2.50]) compared to effectiveness.

Table 4. Comparison of Efficacy Intervention Arms to Effectiveness Intervention Arms

Outcome	Pooled MD (95% CI)	N
SBP (mmHg)	-1.34 (-4.84, 2.15)	21
DBP (mmHg)	- 2.20 (-4.07, -0.34)*	18
Total Cholesterol (mg/dL)	- 1.10 (-11.34, 9.13)	16
HDL Cholesterol (mg/dL)	-0.44 (-2.47, 1.60)	18
LDL Cholesterol (mg/dL)	2.18 (-3.03, 7.38)	13
Triglycerides (mg/dL)	-19.51 (-34.54, -4.48)*	10
Weight (kg)	0.75 (-1.0, 2.50)	19

*Statistically significant result
N: number of study arms included in analysis
MD: mean difference
Note: SBP: systolic blood pressure; DBP: diastolic blood pressure; HDL: high-density lipoprotein; LDL: low-density lipoprotein

In multivariate and univariate meta-regressions, mean age, percent male, duration of intervention, and mean baseline value for the respective outcome were assessed to determine how these predictors affected the relationship between study type (i.e. efficacy versus effectiveness) and effect size. The meta-regressions were performed separately for the two analyses: intervention arms versus control arms, and efficacy versus effectiveness interventions arms.

Duration of intervention was a significant predictor of the difference between intervention and control arms for DBP in efficacy studies (β = -1.0, p = 0.01), and age was a significant predictor of the difference between intervention and control arms for triglycerides in efficacy studies (β = -13.22, p = 0.01). None of the factors were significant predictors of the difference between intervention and control arms in the effectiveness meta-analysis. For the second meta-analysis comparing efficacy and effectiveness interventions arms, higher baseline DBP (β = -0.21, p = 0.02) and higher baseline total cholesterol (β = -0.26, p = 0.04) were significant predictors of the between-arm differences in DBP and

change in total cholesterol, respectively. Baseline DBP and baseline total cholesterol were the only significant predictors of the difference in effect sizes between the efficacy and effectiveness intervention arms.

Study Quality and Publication Bias

Among the 19 efficacy studies, 1 was classified as high-quality, 14 as medium-quality, and 4 as low-quality (5% high, 74% medium, 21% low). Overall, high quality studies were better than low or medium quality studies in regard to blinding for participants and healthcare professionals, lower attrition, using appropriate statistical methods to minimize the impact of attrition, and following CONSORT guidelines for appropriate RCT reporting (30) Egger's tests suggested that publication bias was not present for any of the efficacy outcomes. The funnel plots for both efficacy and effectiveness outcomes are provided in Supplementary Figure S1.

Among the 13 effectiveness studies, 1 was classified as high-quality, 10 as medium-quality, and 2 as low-quality (8% high, 77% medium, 15% low). Overall, high quality studies were better than low or medium quality studies in regard to using objective methods to assess diabetes risk, lower attrition, using intent-to-treat analysis to minimize the impact of attrition, and describing the intervention sufficiently enough to allow transferability to other settings. Egger's tests suggested that publication bias was not present for any of the effectiveness outcomes. The funnel plots are provided in Supplementary Figure S1.

DISCUSSION

The objective of this meta-analysis was to estimate the effect of lifestyle diabetes prevention interventions on cardiovascular outcomes and to explore whether estimates differ

when obtained under highly controlled conditions (i.e. efficacy) than when obtained under real-world conditions (i.e. effectiveness). We found that efficacy studies achieved significant improvements for SBP, DBP, and triglycerides.; while effectiveness studies did not achieve significant improvements for any cardiovascular measures. When we compared the effect sizes of the efficacy intervention arms to effectiveness, we found efficacy intervention arms yielded significantly greater improvements in DBP and triglycerides than effectiveness intervention arms. This meta-analysis shows that interventions delivered under real-world conditions yield smaller yet clinically meaningful effects than efficacy studies and present a cost-effective strategy to improve cardiovascular outcomes.

In efficacy studies, lifestyle modification resulted in improvements for SBP, DBP, and triglycerides. This is similar to effects reported in other meta-analyses and individual studies of lifestyle modification interventions on cardiovascular outcomes (24, 27, 26, 35). The differences in meta-analysis results may be due to differences in characteristics across the studies included in the analysis: study populations (i.e. race, age, level of risk prior to intervention), type of lifestyle intervention, intensity of lifestyle intervention, or time period in which the intervention took place (i.e. including studies conducted from more distantly in the past, such as in Yamaoka and Tango's meta-analysis (35)). Overall, our findings show lifestyle interventions improve cardiovascular outcomes and are useful diabetes preventive interventions.

In effectiveness studies, lifestyle modification interventions did not significantly improve cardiovascular outcomes compared to control arms. Yet, all outcomes improved from baseline to post intervention. This suggests that the interventions likely resulted in clinically meaningful improvements that could impact a person's CVD risk, although the statistical power of the analysis may have limited results. Indeed, other meta-analyses have

demonstrated reductions in SBP, DBP, LDL, triglycerides, and weight (33, 36, 37, 38). A related systematic review and meta-analysis studied DPP-based interventions in real-world settings across the US to explore the impact of the intervention on cardiometabolic risk factors. Similar to the results of other effectiveness meta-analyses, lifestyle modification programs were associated with significant improvements in weight and cardiometabolic measures, including SBP, DBP, HDL, and total cholesterol, achieving similar results to those seen in the DPP. The improvements were achieved despite the barriers common to effectiveness interventions, namely, lower costs and implementation in real-world settings. The authors noted that the translation of an intervention program in real-world settings requires many components to achieve positive impact: referral, uptake, engagement, completion, and post-program sustainability of the outcomes. Moreover, the authors noted that rates of attrition select for the most motivated participants, which leads to bias favoring effectiveness in their meta-analysis. The authors noted that increased uptake and decreased attrition are needed to maximize the impact of lifestyle interventions for patients with diabetes. Overall, the study proved that the findings of the DPP are similar to those found in real-world settings for some of the diabetes-related outcomes, and the authors emphasized the influence of certain factors affecting the effectiveness of lifestyle interventions (33). The findings of this study are similar to the results of our study, which determined that efficacy and effectiveness intervention arms did not have significantly different results for most of the outcomes we reported. In summary, real-world lifestyle interventions can be similarly effective to those seen in efficacy settings, such as clinical trials. However, there are a multitude of factors that contribute to a real-world intervention's effectiveness, and these factors should be prioritized when implementing a healthcare intervention in order to optimize benefit.

When we directly compared the intervention arms of efficacy and effectiveness studies, we found efficacy intervention arms achieved greater improvements in DBP and triglycerides. Efficacy intervention arms also achieved greater effects in SBP and total cholesterol, but these did not differ significantly from those achieved by effectiveness intervention arms. Moreover, effectiveness interventions arms achieved larger effects for HDL and LDL but these results did not differ significantly from the results of the efficacy intervention arms. This comparative analysis suggests that both efficacy and effectiveness studies improve CVD outcomes, but in different magnitudes. For instance, efficacy intervention arms experienced greater improvements for SBP compared to effectiveness, but the difference was not significant: SBP (-1.34 [-4.84, 2.15] mmHg). The differences in effect sizes may be due to population characteristics, intervention settings, and intervention intensity employed in the different studies. For example, efficacy studies included higher risk populations than effectiveness studies (e.g. higher age, higher baseline values), which means that they are more likely to experience significant changes from their pre-intervention measures, since they began with higher values than their lower-risk counterparts in the effectiveness studies. This notion is supported by the differential baseline values between efficacy and effectiveness participants (Table 2) and by the results of the meta-regression, which showed that higher baseline values were associated with greater change between pre- and post-intervention measures. Moreover, compared to effectiveness studies, efficacy studies are more intensive, more strictly implemented, and enforce participant engagement and adherence to intervention (19). Because of these characteristics of efficacy interventions, they tend to yield greater effects for the participants. For instance, in our meta-analysis, the average duration was 2.4 years for efficacy interventions, and 1.7 years for effectiveness interventions. Moreover, the efficacy interventions in our meta-analysis employed more

intensive interventions, such as individualized counseling (58%), dietary and/or exercise plans (22%), and text messages to promote lifestyle modification (5%). In contrast, the majority (69%) of the effectiveness studies employed group education, which is a less intensive form of intervention, while only 23% of the effectiveness studies employed individualized counseling.

A related commentary discussed the implications of the gaps between efficacy and effectiveness interventions for the prevention of type 2 diabetes. The commentary contrasted the results of the DPP, an efficacy-based lifestyle intervention, with the results of MOVE!, a weight program for veterans directed by the Veterans Health Administration (39). The commentary suggested that gaps between the two forms of interventions may be due to low participation in effectiveness studies: in the MOVE! program, only 1% of the eligible cohort, 8% of participants, engaged in intense and sustained intervention. The commentary also notes that the apparent cost-effectiveness seen in efficacy studies, such as the DPP, may no longer be valid when taking into account the low-participation and reduced effectiveness that were seen in the MOVE! Study. In summary, the impact of participation and potential gap in cost-effectiveness should be considered when comparing the results of efficacy and effectiveness lifestyle interventions for the prevention of diabetes (23).

Thus, factors such as attrition, format or technique employed for lifestyle modification interventions, and participant engagement may influence the effectiveness of an intervention. This list is by no means comprehensive, but these examples highlight the complexity of factors that contribute to whether a lifestyle intervention may effectively improve cardiovascular outcomes in diabetes prevention interventions. These factors should be considered during the development and implementation of a lifestyle intervention for the prevention of diabetes.

Limitations

Although we have conducted a robust and comprehensive analysis comparing efficacy and effectiveness of diabetes prevention lifestyle interventions on cardiovascular outcomes, there are limitations to our study. We did not update our search after the initial searches were conducted for the original efficacy and effectiveness meta-analyses, which were last updated in 2015. Additionally, we found a high level of heterogeneity for some of the effects, suggesting that there were other factors affecting treatment intervention effects that we did not account for. Another limitation is that we did not compare the effects between types of intervention, i.e. individualized versus group, or compare between different races/ethnicities. Moreover, the original search terms used were in English, which may have prevented certain studies from being identified that were in other languages.

CONCLUSIONS

In a direct comparison of lifestyle interventions in two different study settings, interventions conducted under highly controlled conditions improved more for DBP, triglycerides (both significant improvements), SBP, and total cholesterol, while those conducted under real-world conditions improved more for HDL, LDL, and weight. When these two forms of interventions were compared to their control arms, efficacy interventions demonstrated significantly better results for SBP, DBP, and triglycerides, while effectiveness interventions did not show any significant differences from their control arms.

Efficacy studies had larger effects than effectiveness, but effectiveness still showed improvements in cardiovascular outcomes and weight compared to efficacy studies. This proves that effectiveness studies have real-world impact and validity. However, it is essential

that effectiveness studies be implemented in such a way that they achieve the same effects as those seen in efficacy studies. The purpose of healthcare research is to improve human health in the real world, but this cannot be achieved if the results seen in highly-controlled efficacy studies are not applicable to real-world settings. Thus, future studies should focus on identifying additional factors that contribute to the gap between efficacy and effectiveness studies. Additionally, future studies should aim to identify methods and tools that can be used to mitigate the discrepancy. In doing so, real-world interventions can achieve similar results to those achieved in clinical trials and other efficacy-based studies.

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Appendix

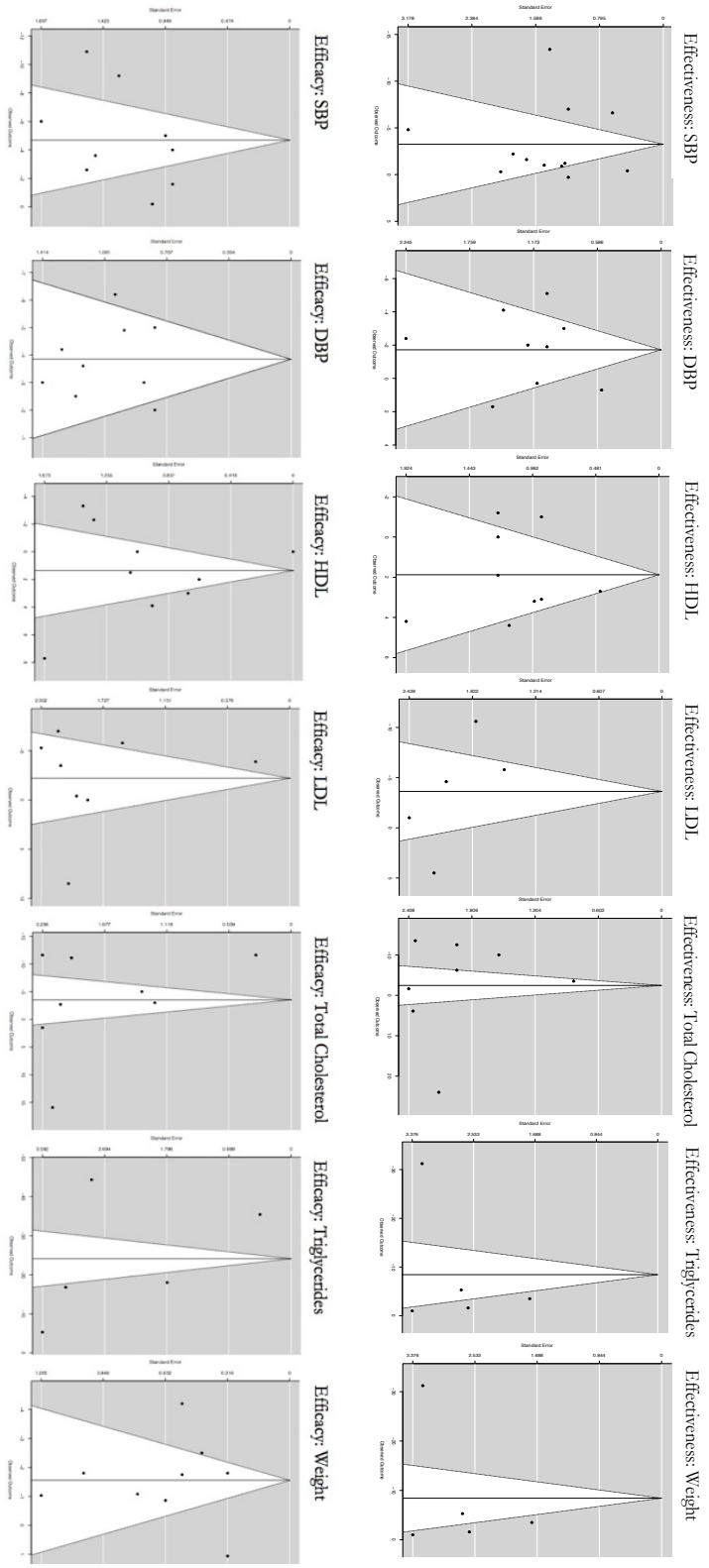

Figure S1. Funnel Plots Representing Heterogeneity Among Study Outcomes