

Long-term Sustainability of Diabetes Prevention Approaches

A Systematic Review and Meta-analysis of Randomized Clinical Trials

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[+ Supplemental content](#)

IMPORTANCE Diabetes prevention is imperative to slow worldwide growth of diabetes-related morbidity and mortality. Yet the long-term efficacy of prevention strategies remains unknown.

OBJECTIVE To estimate aggregate long-term effects of different diabetes prevention strategies on diabetes incidence.

DATA SOURCES Systematic searches of MEDLINE, EMBASE, Cochrane Library, and Web of Science databases. The initial search was conducted on January 14, 2014, and was updated on February 20, 2015. Search terms included *prediabetes*, *primary prevention*, and *risk reduction*.

STUDY SELECTION Eligible randomized clinical trials evaluated lifestyle modification (LSM) and medication interventions (>6 months) for diabetes prevention in adults (age ≥ 18 years) at risk for diabetes, reporting between-group differences in diabetes incidence, published between January 1, 1990, and January 1, 2015. Studies testing alternative therapies and bariatric surgery, as well as those involving participants with gestational diabetes, type 1 or 2 diabetes, and metabolic syndrome, were excluded.

DATA EXTRACTION AND SYNTHESIS Reviewers extracted the number of diabetes cases at the end of active intervention in treatment and control groups. Random-effects meta-analyses were used to obtain pooled relative risks (RRs), and reported incidence rates were used to compute pooled risk differences (RDs).

MAIN OUTCOMES AND MEASURES The main outcome was aggregate RRs of diabetes in treatment vs control participants. Treatment subtypes (ie, LSM components, medication classes) were stratified. To estimate sustainability, post-washout and follow-up RRs for medications and LSM interventions, respectively, were examined.

RESULTS Forty-three studies were included and pooled in meta-analysis (49 029 participants; mean [SD] age, 57.3 [8.7] years; 48.0% [n = 23 549] men): 19 tested medications; 19 evaluated LSM, and 5 tested combined medications and LSM. At the end of the active intervention (range, 0.5-6.3 years), LSM was associated with an RR reduction of 39% (RR, 0.61; 95% CI, 0.54-0.68), and medications were associated with an RR reduction of 36% (RR, 0.64; 95% CI, 0.54-0.76). The observed RD for LSM and medication studies was 4.0 (95% CI, 1.8-6.3) cases per 100 person-years or a number-needed-to-treat of 25. At the end of the washout or follow-up periods, LSM studies (mean follow-up, 7.2 years; range, 5.7-9.4 years) achieved an RR reduction of 28% (RR, 0.72; 95% CI, 0.60-0.86); medication studies (mean follow-up, 17 weeks; range, 2-52 weeks) showed no sustained RR reduction (RR, 0.95; 95% CI, 0.79-1.14).

CONCLUSIONS AND RELEVANCE In adults at risk for diabetes, LSM and medications (weight loss and insulin-sensitizing agents) successfully reduced diabetes incidence. Medication effects were short lived. The LSM interventions were sustained for several years; however, their effects declined with time, suggesting that interventions to preserve effects are needed.

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Diabetes is a burdensome, costly disease affecting 415 million adults globally, with projections of 642 million adults affected by 2040.¹ Diabetes is the leading cause of end-stage renal failure, adult-onset blindness, and nontraumatic amputations and significantly contributes to cardiovascular morbidity and mortality.² Treatment costs of type 2 diabetes (subsequently referred to as *diabetes*) remain a significant burden on individuals and health care systems, amounting to \$245 billion in the United States alone in 2012.³ Primary prevention of diabetes has proved to be cost-effective in various populations and settings³ and is therefore crucial to reducing growing diabetes burdens. Yet, translating these findings into practice remains a major challenge.

Although many studies have tested different diabetes prevention interventions, data remain discordant on which modalities offer long-term efficacy. Previous reviews and meta-analyses have reported that both lifestyle modification (LSM) (ie, physical activity and dietary changes) and medications are beneficial in preventing progression to diabetes, but there are conflicting results regarding which type, frequency, and intensity of LSM or medications are most enduring that would inform clinical practice.⁴⁻⁸ Lack of evidence on the long-term efficacy of diabetes prevention interventions may compromise policy-making guidance. The need for such guidance is especially important as several countries embark on national diabetes prevention programs.^{9,10}

To deliver more granular direction in such efforts, this systematic review and meta-analysis provides an updated, rigorous evaluation of a large number of studies with comprehensive analysis of long-term efficacy of various nonsurgical diabetes prevention strategies using data from randomized clinical trials.

Methods

Data Sources and Searches

We searched MEDLINE, EMBASE, Cochrane Library, and Web of Science databases for eligible articles published and indexed from January 1, 1990, to January 1, 2015. We used combinations of Medical Subject Headings and search terms, such as *prediabetes*, *primary prevention*, and *risk reduction* (full search strategy available in eTable 1 in the [Supplement](#)). There was no restriction on language of publication, and non-English articles were translated. We undertook the initial search on January 14, 2014, and performed an updated search on February 20, 2015. All publications were screened for eligibility independently by 2 of us (J.S.H., M.J.M.), with disagreements resolved by another one of us (M.K.A.). We adhered to PRISMA reporting guidelines for this systematic review and meta-analysis.¹¹ No patients were directly involved in this meta-analysis.

Study Selection

We included published randomized clinical trials testing the efficacy of diabetes prevention interventions lasting at least 6 months in adults (age ≥ 18 years) with prediabetes, defined by either impaired glucose tolerance (IGT), impaired fasting

Key Points

Questions How much do primary prevention strategies reduce the risk of conversion from prediabetes to diabetes, and are initial effects sustained over the long term?

Findings In this meta-analysis of randomized clinical trials including 49 029 participants, lifestyle modification and medications promoting weight loss or insulin sensitization were associated with reduced diabetes risk by 36% to 39%. Effects of medications were not sustained after they were discontinued; effects of lifestyle modification, however, were sustained after intervention was stopped, although the effects waned over time.

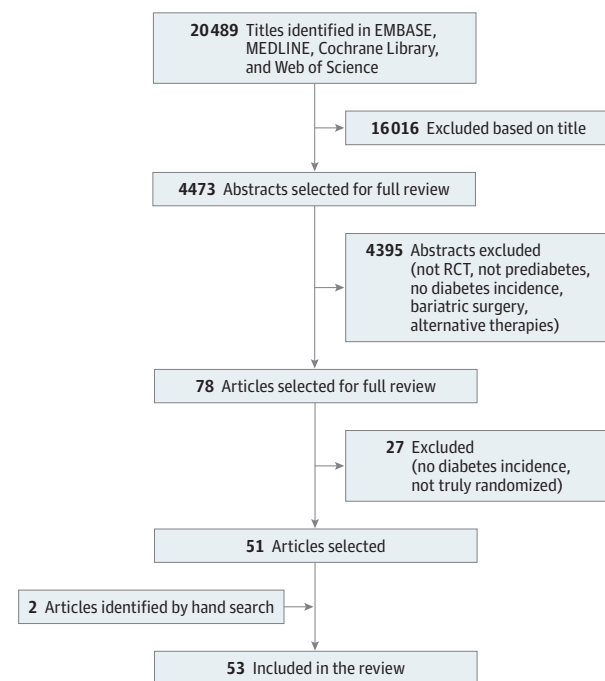
Meaning For individuals at risk for diabetes, healthy lifestyle changes, weight loss, or use of insulin-sensitizing medications slow the progression to diabetes similarly; lifestyle modification strategies are better in the long term, although strategies to maintain their effects are needed.

glucose (IFG), or both, using diagnostic criteria according to the American Diabetes Association (1997 and 2003)^{12,13} or World Health Organization (1985, 1999, or 2006)^{14,15} and reporting between-treatment group differences in diabetes incidence rates. Diabetes was defined according to American Diabetes Association or World Health Organization criteria, which differed slightly depending on the year the study was performed, but all trials used either oral glucose tolerance tests and/or fasting plasma glucose levels to diagnose diabetes. We excluded studies involving individuals with type 1 or 2 diabetes, gestational diabetes, metabolic syndrome (where prediabetes status was not confirmed), and age younger than 18 years. We also excluded studies evaluating alternative therapies due to the large heterogeneity and lack of data on active ingredients or their potential physiologic effects. We excluded bariatric surgeries given the distinctive nature of these interventions, rigid inclusion criteria, and cost.

Data Extraction

From the identified studies, we extracted or calculated the number of persons who developed diabetes at the end of the active intervention period and, when reported, at the end of the washout or follow-up periods (ie, time when participants were observed after discontinuing interventions). Participant characteristics (eg, age, sex, and body mass index) and study characteristics (eg, sample size, treatment duration) were also extracted. Data were obtained using standardized abstraction templates. When the results of a study were reported in multiple publications, data from all publications were extracted under a single study identity and used for different subgroup analyses. In studies including mixed cohorts of people with prediabetes and diabetes or metabolic syndrome, we extracted data only for the prediabetes cohort. Thirty authors were contacted 1 to 5 times to clarify or obtain unpublished data required for our meta-analysis. Efforts were made to contact authors who had changed affiliation and contact information since publication. Of these, 6 authors provided additional data; in cases in which authors did not respond, we used data reported to calculate the needed values or did not include the study in the analyses.

Figure 1. Study Screening and Selection Flow



Overview of study screening and selection process according to PRISMA guidelines. RCT indicates randomized clinical trial.

Quality Assessment

To assess the quality of studies, we used a set of quality indicators adapted from those proposed by Jadad et al.¹⁶ The first indicator was blinding: whether the study blinded participants or health care professionals (1 point), both (2 points), or neither (0 points). The second indicator was attrition: whether an attrition rate of less than 20% (2 points), over 20% (1 point), or differential attrition between groups (0 points) was reported. The third indicator was statistical methods used to minimize the impact of attrition if intent-to-treat analysis (2 points) or per protocol (1 point) were applied, or if none were reported (0 points). Since all of our studies were randomized clinical trials, we replaced the random allocation indicator by a fourth indicator assessing whether CONSORT guidelines were used for appropriate randomized clinical trial reporting (2 points),¹⁷ no guidelines were used but reporting was clear (1 point), or reporting was unclear (0 points). Scores were summed to obtain composite quality scores for each study. Studies scoring 0 to 3 points were classified as low quality, 4 to 6 as medium quality, and 7 to 8 as high quality.

Statistical Analysis

We used random-effects meta-analysis models to account for heterogeneity between studies.¹⁸ For trials reporting zero events in 1 of the study arms, we used a continuity correction of 0.5. We estimated the aggregate relative risk (RR) for diabetes achieved at the end of active intervention in LSM and medication trials separately. We estimated aggregate RRs for different subtypes of LSM strategies (ie, diet, physical activ-

ity, or combined) and medication subclasses (eg, insulin sensitizers, insulin secretagogues). To explore intervention effects after treatment withdrawal, we estimated the aggregate RR for diabetes at the end of active intervention and at the end of the washout period for medication trials or at the end of the follow-up period for LSM trials.

We estimated heterogeneity across studies by computing I^2 , where I^2 greater than 75% indicated significant heterogeneity. We used meta-regressions to explore the contribution of participant demographic characteristics and weight change to intervention effect heterogeneity.¹⁸ We assessed publication bias using the Egger test and visual exploration of funnel plots. The number of studies with null effects that were missing from the meta-analysis was estimated using the trim-and-fill method.¹⁹ Sensitivity analyses were conducted according to study quality category (low, medium, and high) to explore the risk of bias on the meta-analytic estimates. The metafor package²⁰ in R, version 3.2.1 programming language was used to fit the models described.

Results

Study Characteristics

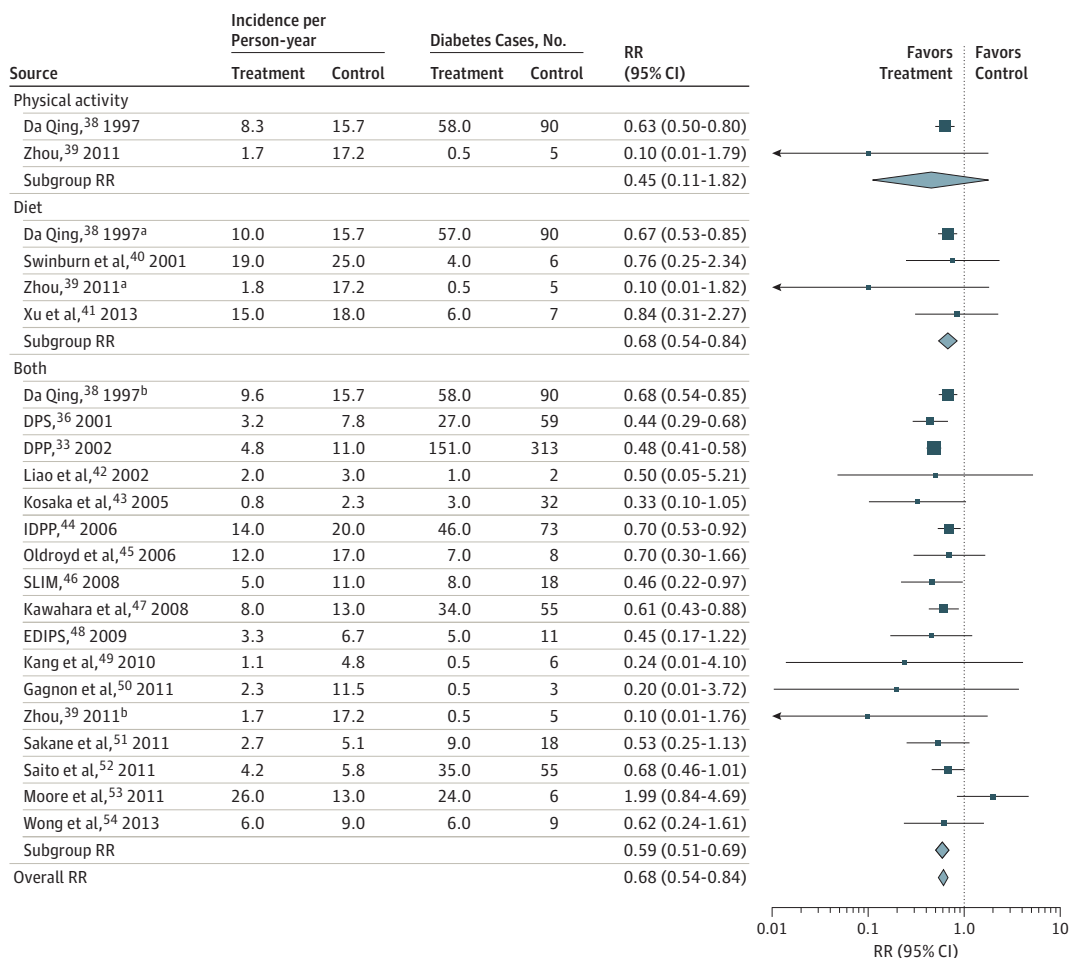
Of the 20 489 titles identified, 4473 abstracts were reviewed and 78 published articles were selected for full review. Of these, 51 articles were included, and 2 additional articles were identified manually.^{21,22} Overall, 53 articles were included in the systematic review (Figure 1). Of the included articles, 10 were not meta-analyzed because they either did not report the number of participants who developed diabetes at the end of the study ($n = 3$),²³⁻²⁵ did not report the number of people at risk for diabetes at baseline in each arm ($n = 1$),²⁶ reported findings from a trial that was already included in the analyses ($n = 5$),²⁷⁻³¹ or tested a drug (troglitazone) that has been discontinued ($n = 1$).³² Forty-three articles reported sufficient data for meta-analyses, and, based on quality assessment, data pooling was deemed appropriate among these studies.

Of the studies analyzed, 19 evaluated single or multiple medications, 19 tested LSMs, and 5 tested both medication and LSMs. Forty studies had a total follow-up length ranging from 0.5 to 6.3 years, while the US Diabetes Prevention Program (DPP),^{33,34} the Finnish Diabetes Prevention Study (DPS),^{35,36} and the Da Qing Diabetes Prevention Study (Da Qing)^{37,38} reported follow-up lengths of 10, 13, and 20 years since randomization, respectively. The total number of participants across studies was 49 029 (mean [SD] age, 57.3 [8.7] years; 23 549 [48.0%] men; baseline body mass index, 30.8 [calculated as weight in kilograms divided by height in meters squared]) and included Asian, North American, and European participants (eTable 2 in the Supplement).

Efficacy of LSM Interventions

During the active intervention period (mean [SD], 2.6 [1.7] years; range, 0.5-6.0 years), LSM studies ($n = 19$) achieved an RR reduction of 39% (RR, 0.61; 95% CI, 0.54-0.68). Diabetes incidence rates in intervention participants were 7.4 cases per 100 person-years compared with 11.4 cases per 100 person-years in

Figure 2. Relative Risks (RRs) and Diabetes Incidence Rates Among Lifestyle Modification Intervention Studies Stratified by Intervention Strategy at the End of the Active Intervention Period



Nineteen studies including 24 comparisons were analyzed. Active intervention mean (SD) duration was 2.6 (1.7) years (range, 0.5-6.0 years). Overall RR is the pooled effect for all studies; subgroup RR is the pooled effect for a subgroup of studies. DPP indicates Diabetes Prevention Program; DPS, Diabetes Prevention Study; EDIPS, European Diabetes Prevention Study;

IDPP, Indian Diabetes Prevention Programme; and SLIM, Study on Lifestyle-Intervention and Impaired Glucose Tolerance Maastricht.
^a Second arm of the same study.
^b Third arm of the same study.

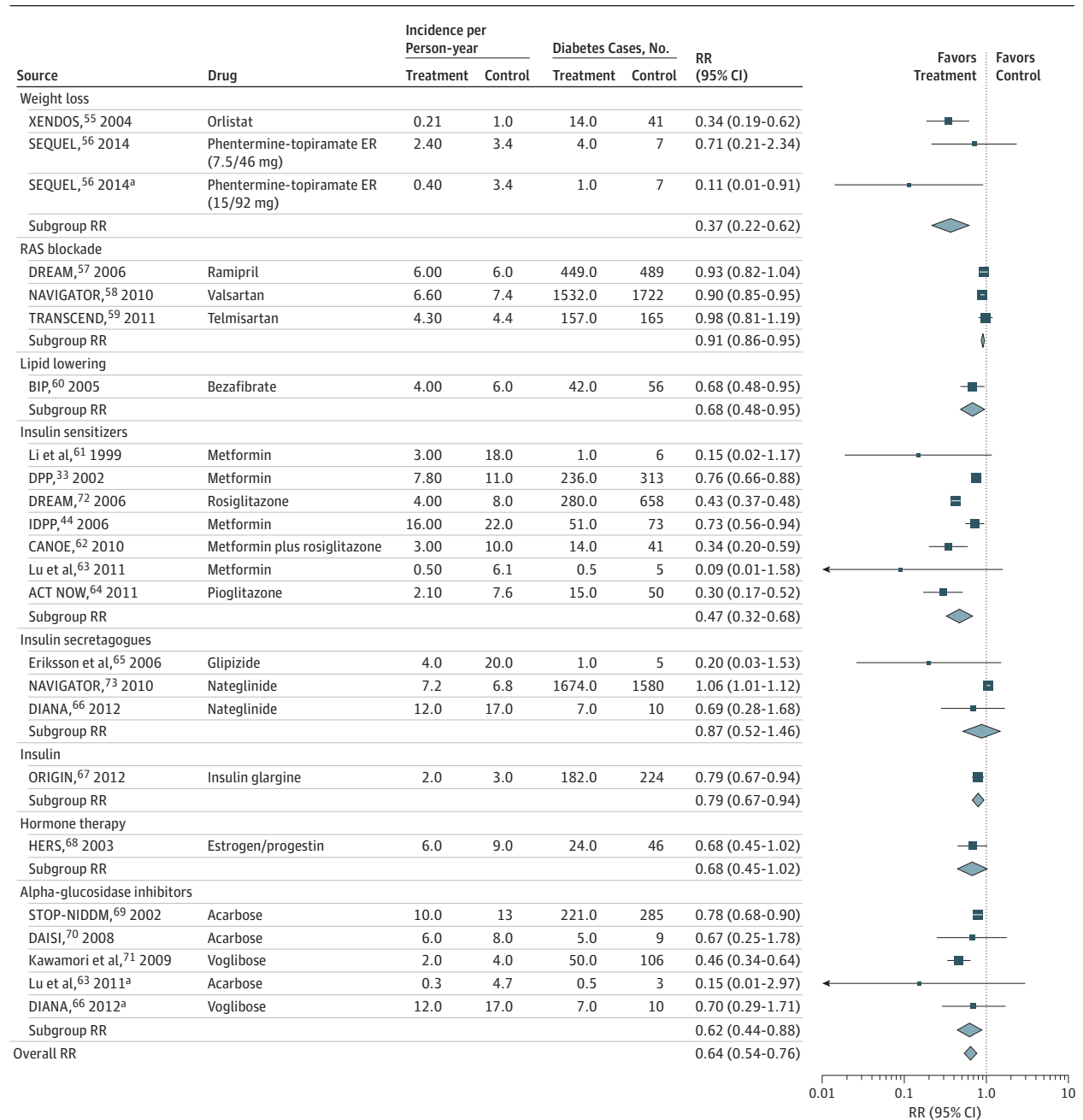
control participants (risk difference [RD], 4.0; 95% CI, 1.8-6.3). Overall, 25 persons would need to be treated with LSM to prevent 1 case of diabetes. The DPP,³³ DPS,³⁶ and Da Qing³⁸ studies achieved the largest RR reductions (Figure 2).^{33,36,38-54} Using dietary strategies alone was associated with a 32% RR reduction (RR, 0.68; 95% CI, 0.54-0.84) in diabetes incidence, albeit only counseling with individualized diet plans achieved significant effects (RR, 0.67; 95% CI, 0.53-0.85). Using physical activity interventions alone (n = 2) did not significantly reduce the risk for diabetes except in the Da Qing study,³⁸ which implemented individualized exercise plans (RR, 0.63; 95% CI, 0.50-0.80). Combined diet and physical activity strategies achieved a 41% RR reduction (RR, 0.59; 95% CI, 0.51-0.69).

Efficacy of Medication Interventions

During the active intervention period (mean [SD], 3.1 [1.5] years; range, 1.0-6.3 years), medication trials (n = 21; 18

medication and 3 LSM plus medication trials) achieved an RR reduction of 36% (RR, 0.64; 95% CI, 0.54-0.76). Diabetes incidence rates in intervention participants were 5.4 cases per 100 person-years compared with 9.4 cases per 100 person-years in control participants (RD, 4.0; 95% CI, 2.3-5.7). Overall, 25 persons would need to be treated to prevent 1 case of diabetes. Weight loss drugs (orlistat, combination phentermine-topiramate) achieved the largest RR reduction of 63% (RR, 0.37; 95% CI, 0.22-0.62) (Figure 3).^{33,44,55-73} Insulin sensitizers (metformin, rosiglitazone, and pioglitazone) achieved an RR reduction of 53% (RR, 0.47; 95% CI, 0.32-0.68). Among renin-angiotensin system blockade drugs, only valsartan achieved a significant 10% RR reduction (RR, 0.90; 95% CI, 0.85-0.95). α-Glucosidase inhibitors (acarbose, voglibose) achieved a 38% RR reduction (RR, 0.62; 95% CI, 0.44-0.88), with 2 studies showing significant effects and 3 studies showing no effects. A lipid-lowering

Figure 3. Relative Risks (RRs) and Diabetes Incidence Rates Among Medication Studies Stratified by Drug Class at the End of the Active Intervention Period



Twenty-one studies including 24 comparisons were analyzed. Active treatment mean (SD) duration was 3.1 (1.5) years (range, 1.0-6.3 years). Overall RR is the pooled effect for all studies; subgroup RR is the pooled effect for a subgroup of studies. ACE indicates angiotensin-converting enzyme; ACT NOW, Actos Now for Prevention of Diabetes; BIP, Bezafibrate Infarction Prevention Study; CANOE, Canadian Normoglycemia Outcomes Evaluation; DAISI, Dutch Acarbose Intervention Study in Persons With Impaired Glucose Tolerance; DIANA, Diabetes and Diffuse Coronary Narrowing; DPP, Diabetes Prevention Program; DREAM, Diabetes Reduction Assessment With Ramipril and Rosiglitazone Medication; ER, extended release; HERS, Heart and

Estrogen/progestin Replacement Study; IDPP, Indian Diabetes Prevention Programme; NAVIGATOR, Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research; ORIGIN, Outcome Reduction With Initial Glargine Intervention; RAS, renin-angiotensin system; STOP-NIDDM, Study to Prevent Non-Insulin-Dependent Diabetes Mellitus; TRANSCEND, Telmisartan Randomised Assessment Study in ACE Intolerant Subjects With Cardiovascular Disease; and XENDOS, Xenical in the Prevention of Diabetes in Obese Subjects.

^a Second arm of the same study.

drug (bezafibrate) and insulin analogue (glargine) achieved RR reductions of 32% (RR, 0.68; 95% CI, 0.48-0.95) and

21% (RR, 0.79; 95% CI, 0.67-0.94), respectively. Hormone therapy (estrogen and progestin) and insulin secretagogues

Table. Random-Effects Meta-analyses Exploring RR for Diabetes Among LSM and Medication Studies After Treatment Withdrawal

Source	Intervention	Active Intervention, y	End of Active Intervention, RR (95% CI)	Follow-up ^a	End of Follow-up, RR (95% CI)
LSM Trials					
Swinburn et al, ⁴⁰ 2001	Reduced-fat diet	1.0	0.76 (0.25-2.34)	5.0 y	0.70 (0.26-1.88)
DPP, ^{33,34} 2002, 2009 ^b	Diet and physical activity	2.8	0.48 (0.41-0.58)	5.7 y	0.68 (0.63-0.73)
DPS, ^{35,36} 2001, 2013	Diet and physical activity	4.0	0.44 (0.29-0.68)	9.0 y	0.63 (0.54-0.73)
Da Qing, ^{37,38} 1997, 2008	Diet and physical activity	6.0	0.68 (0.54-0.85)	9.4 y	0.86 (0.81-0.92)
Pooled estimate			0.55 (0.43-0.70)		0.72 (0.60-0.86)
Medication Trials					
Eriksson et al, ⁶⁵ 2006	Glipizide	0.5	0.41 (0.01-11.3)	52 wk	0.20 (0.03-1.53)
DREAM, ^{22,72} 2006, 2011	Rosiglitazone	3.0	0.43 (0.37-0.48)	10 wk	1.07 (0.88-1.32)
DREAM, ^{22,57} 2006, 2011 ^b	Ramipril	3.0	0.93 (0.82-1.04)	10 wk	1.08 (0.89-1.33)
DPP, ^{21,33} 2002, 2003	Metformin	2.8	0.76 (0.66-0.88)	2 wk	0.76 (0.68-0.85)
STOP-NIDDM, ⁶⁹ 2002	Acarbose	3.0	0.78 (0.68-0.90)	12 wk	1.46 (0.90-2.36)
ORIGIN, ⁶⁷ 2012	Insulin glargine	6.2	0.79 (0.67-0.94)	14 wk	0.86 (0.74-0.99)
Pooled estimate			0.71 (0.55-0.92)		0.95 (0.79-1.14)

Abbreviations: DPP, Diabetes Prevention Program; DPS, Diabetes Prevention Study; DREAM, Diabetes Reduction Assessment With Ramipril and Rosiglitazone Medication; LSM, lifestyle modification; ORIGIN, Outcome Reduction With Initial Glargine Intervention; RR, relative risk; STOP-NIDDM, Study to Prevent Non-Insulin-Dependent Diabetes Mellitus.

^a Duration of observation period after participants completed the intervention or stopped the medication.

^b Control arm received LSM intervention after the active intervention period, which likely minimizes the between-group difference that might have been observed.

(glipizide, nateglinide) were not associated with significant RRs in diabetes incidence.

Sustainability of Diabetes Prevention

To explore whether diabetes prevention effects were sustained after treatment withdrawal, we estimated the RR for diabetes at the end of the intervention and at the end of the washout or follow-up periods among studies reporting these data (5 testing medications, 3 testing LSM, and 1 testing LSM and medication) (Table). Of medication trials, 2 tested insulin sensitizers (metformin, rosiglitazone),^{21,22,33,72} 1 evaluated an insulin secretagogue (glipizide),⁶⁵ and the remaining 3 tested a renin-angiotensin system blockade,^{22,57} α -glucosidase inhibitor,⁶⁹ and insulin.⁶⁷ The mean observation periods for washouts across these studies was 17 weeks (range, 2-52 weeks). Compared with those receiving placebo, participants receiving the study drug had a 29% lower diabetes risk at the end of the active intervention (RR, 0.71; 95% CI, 0.55-0.92), while no significant RR reductions were observed at the end of the washout period (RR, 0.95; 95% CI, 0.79-1.14). Of LSM trials, 4 (DPP,^{33,34} Da Qing,^{37,38} DPS,^{35,36} and Swinburn et al⁴⁰) provided follow-up data. Only the DPP trial implemented strategies to maintain lifestyle changes and offered the LSM intervention to control participants during the postintervention observation period. The mean follow-up duration across these studies was 7.2 years (range, 5.7-9.4 years). Compared with control participants, those receiving LSM intervention had a 45% lower diabetes risk at the end of the active intervention period (RR, 0.55; 95% CI, 0.43-0.70) and a 28% lower risk at the end of the follow-up period (RR, 0.72; 95% CI, 0.60-0.86).

Heterogeneity and Study Quality

Studies were heterogeneous, leading to a high proportion of variability between study effects. Heterogeneity was larger for medication (I^2 range, 0%-89%) than LSM (I^2 range, 0%-36%) studies. In a multivariate meta-regression, amount of weight lost, participant mean age, and proportion of male participants accounted for 59% of the heterogeneity ($P < .01$). In this model, only weight lost was significantly associated with diabetes risk, in which every kilogram lost explained an additional 7% decrease in diabetes relative risk ($\beta = -0.07$; $P < .01$) (eFigure 1 in the Supplement).

Of the 43 pooled studies, 38 were unique trials and 5 were reports of different follow-up periods of studies already included. Of the 38 unique studies, 11 were classified as high-quality, 22 as medium-quality, and 5 as low-quality. In sensitivity analyses, high-, medium-, and low-quality studies showed similar RR reductions ranging from 35% in high-quality (RR, 0.65; 95% CI, 0.50-0.84), 37% in medium-quality (RR, 0.63; 95% CI, 0.54-0.73), and 42% in low-quality (RR, 0.58; 95% CI, 0.41-0.81) studies.

We found evidence of publication bias ($t = -4.1_{39}$; $P < .001$), and visual examination of the funnel plot showed that studies with small or null effects were less likely to be published (eFigure 2 in the Supplement). The trim-and-fill test demonstrated that approximately 9 studies with null effects were missing, and sensitivity analysis showed that, if included, diabetes RR reduction would be smaller (33% vs 36%), albeit still significant ($P < .001$). When examined individually, no study was found to significantly influence aggregate estimates.

Discussion

This meta-analysis shows that LSM and certain medications are effective in preventing diabetes in persons at risk, although only LSM strategies seem to have a sustainable effect. Diet with physical activity or weight loss and insulin-sensitizing medications prevent progression to diabetes in individuals at risk, with 25 persons needing to be treated to prevent a single diabetes case. Across all interventions, weight loss appears to be the key factor associated with reduced diabetes progression.

Our findings show that LSM interventions are efficacious for preventing diabetes. The RR reduction that we observed in LSM interventions is similar to estimates from other meta-analyses.^{4,8} Combined diet alterations and physical activity proved to be more effective in reducing progression to diabetes than either strategy alone. Since caloric intake and physical activity are independently associated with reduced diabetes risk, combining these may exert an additive effect.

Medications are efficacious in preventing diabetes in those at risk in the short term, although they present with wide variations depending on the class of medication; these results are similar to those from previous meta-analyses.^{4,6,8} Our study expands this evidence by including combined phentermine-topiramate, a newer antiobesity drug.⁵⁶ We showed that weight-loss medications, followed by insulin sensitizers, achieved the greatest diabetes risk reductions. Newer US Food and Drug Administration–approved weight loss medications (eg, liraglutide, combined naltrexone-bupropion) may also slow progression to diabetes, although studies testing these drugs were pending at the time of our literature search. Insulin sensitizers, such as the glitazones and metformin, have shown efficacy for diabetes prevention in other meta-analyses.^{4,5,8} We found mixed or small effects of α -glucosidase inhibitors and renin-angiotensin system blockers, indicating insufficient evidence to make firm conclusions.

To our knowledge, this is the first meta-analysis to explore the long-term effects of diabetes prevention interventions after treatment withdrawal. We found that participants receiving LSM interventions had lower risk for diabetes than control participants 5 to 9 years after completing the intervention, although the effects decreased over time. However, our aggregate findings regarding the durability of LSM may also be considered conservative since the control arm of DPP received the intervention when the trial was prematurely stopped; therefore, all long-term, between-group differences are smaller than if the control participants had not received any intervention. The 15-year follow-up results of the DPP found a similar waning of effects after the initial 2.8 years of active intervention,⁷⁴ suggesting plateauing of effects or saturation among at-risk individuals as most have already progressed to diabetes. This diminished effect also suggests that maintenance strategies, such as those tested in the DPP, may be needed to sustain intervention effects. Regarding the sustainability of medication effects, our analysis using washout data showed that the initial effects of medications dissipated after the washout period. This finding suggests that medica-

tions do not permanently alter fundamental pathophysiology of insulin resistance or β -cell dysfunction and likely only suppress hyperglycemia for the time that they are administered. No weight loss medications were included in this subgroup analysis, indicating a need for further studies on the long-term effects of weight loss medications on both weight lost and regained and their effects on future diabetes incidence. Overall, our findings suggest that LSM interventions are promising long-term diabetes prevention strategies; however, maintenance interventions, even if intermittent, may be needed for prolonged intervention effects.

We found that every kilogram of weight lost was associated with an additional 7% decrease in risk of progression to diabetes. Other systematic reviews and meta-analyses have shown variable effects of weight loss on the incidence of diabetes, reporting positive and null effects.^{4,7,8} Physiologically, it has been shown that losing weight depletes free fatty acids from both muscle and liver, resulting in improved insulin sensitivity and glucose homeostasis.⁷⁵ Additional research has demonstrated that obesity-induced β -cell dysfunction can be restored with caloric restriction and reversion to normal weight in overweight and obese individuals.⁷⁶ The long-term effect in insulin resistance and β -cell dysfunction associated with weight lost due to lifestyle changes vs medications vs bariatric surgery requires further investigation.

Overall, the evidence that this meta-analysis provides is strong given that all of the studies used randomized clinical trial study designs and 79% of the included studies were deemed as having low risk of bias (ie, they were medium to high quality). However, we found evidence of publication bias, which means that smaller studies with null effects were less likely to be published. Countries that plan to launch national diabetes prevention programs should consider modeling their strategies after LSM interventions proven to prevent diabetes, such as the DPP, DPS, and Da Qing, and to implement strategies to sustain long-term effects. Gaps that remain include exploring intervention effects according to glucose intolerance type (ie, IFG vs IGT), publishing studies with null effects, and economic evaluations of long-term maintenance strategies. Future studies and meta-analyses should consider addressing these gaps.

Limitations

Although we provide a comprehensive, rigorous meta-analysis on the efficacy of diabetes prevention treatments, this study has some limitations. We found a high level of heterogeneity in treatment effects, which was only partially explained in meta-regressions and subgroup analyses. This heterogeneity suggests that there are other factors affecting treatment efficacy that were not accounted for, which may involve the pooling of both IFG and IGT definitions of prediabetes. Comparisons among studies require caution given that various definitions of diabetes were used in the trials (eg, World Health Organization 1985, 1999, and 2006; American Diabetes Association 1997, 2003), although they were used consistently within each trial. Another limitation is that we did not directly compare the efficacy of LSM against that of medications; a network meta-analysis is required for such

comparison. Finally, we used English search terms, which may have prevented us from finding studies published in other languages.

Conclusions

Our study demonstrates that diabetes can be prevented in those at risk through multiple LSM strategies and certain medication classes, allowing health care professionals to individualize preventive care appropriate to community resources, individual motivations, and coverage for various interventions. Combined diet and physical activity programs and use of in-

ulin-sensitizing and weight-loss medications achieve the largest diabetes risk reductions. Overall, LSM strategies provide better long-term effects than medications, although strategies to sustain intervention effects are needed. As intervention effects decrease over time, future research should identify cost-effective, successful maintenance strategies to prevent or delay progression to diabetes. Additionally, more studies identifying the differences in intervention effects for those with isolated IGT, isolated IFG, or both are needed to develop better individualized prevention approaches. Dissemination and real-world implementation of LSM with strategies for long-term sustainability on a large-scale is critical in addressing the global diabetes burden.

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