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Interventions for Reversing Prediabetes: A Systematic Review and Meta-Analysis

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Abstract

Introduction: Several interventions have been found to be effective for reversing prediabetes in adults. This systematic review and meta-analysis aims to compare the effectiveness of such interventions.

Methods: MEDLINE, Embase, and Cochrane Library databases were searched for articles published between January 1, 2000 and June 27, 2018. RCTs in adults with prediabetes, testing non-surgical interventions lasting 3 months, and reporting the number of participants achieving normal glucose levels at intervention end were eligible. The pooled risk difference (RD) and number needed to treat (NNT) for achieving normoglycemia were estimated using a random-effects, arm-based network meta-analysis. The strength of the evidence was assessed using Grading of Recommendations Assessment, Development, and Evaluation. Data were obtained in 2018 and analyzed in 2019 and 2021.

Results: Of 54 studies included in the systematic review, 47 were meta-analyzed ($n=26,460$, mean age=53 years, 46% male, 31% White). Studies included 27 arms testing lifestyle modification interventions, 25 medications, 5 dietary supplements, and 10 Chinese medicine. There were 35 control/placebo arms. At a median follow-up of 1.6 years, more participants in the lifestyle modification groups achieved normoglycemia than control (RD=0.18, NNT=6). The strength of the evidence was strong for lifestyle modification. Over a median follow-up of 2.7 years, more participants receiving glucagon-like peptide-1 receptor agonists (RD=0.47, NNT=2), alpha-glucosidase inhibitors (RD=0.29, NNT=4), and insulin sensitizers (RD=0.23,

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NNT=4) achieved normoglycemia than control. The strength of evidence was moderate for these medications.

Discussion: Though several pharmacological approaches can reverse prediabetes, lifestyle modification provides the strongest evidence of effectiveness and should remain the recommended approach to address this condition.

INTRODUCTION

Prediabetes is a state of impaired glucose regulation where blood glucose levels are elevated but do not reach type 2 diabetes thresholds.¹ Though the true global burden of prediabetes is likely unknown, current estimates suggest the global prevalence ranges from 8% to 58%, depending on which diagnostic cut offs are employed.^{2,3} People with prediabetes have increased risk for mortality, cardiovascular disease, and renal disease,⁴⁻⁹ even if they do not develop diabetes. Overall, prediabetes represents a substantial economic burden for current healthcare expenditure¹⁰ and a potential future increase in diabetes healthcare costs.

There is evidence that lifestyle modification, some medications, and alternative medicine can reverse prediabetes in adults. Specifically, alpha-glucosidase inhibitors (AGIs), thiazolidinediones, Chinese medicine, vitamin D, and improvements in physical activity and dietary behaviors have been found to be effective for reversing prediabetes.¹¹⁻¹⁵ This has significant health benefits. In China, the 20-year follow up of the Daqing diabetes prevention study showed participants who returned to normal glucose levels during the intervention had lower diabetes incidence rates than those who remained in the prediabetes state.¹⁶ Another study from China showed adults with prediabetes who returned to normal glucose levels had lower risk for cardiovascular events than those who progressed to diabetes.¹⁷ In the U.S., the Diabetes Prevention Program Outcomes Study showed reversion to normal glucose regulation was associated with lower diabetes incidence and a lower prevalence of microvascular complications.¹⁸⁻²⁰

It remains unknown which treatments or interventions are most effective for reversing prediabetes. To answer this question, this study aims to synthesize and compare the effectiveness of diverse interventions for reverting prediabetes to normal glucose regulation that were tested via RCTs. This study could inform policy and practice directed at managing prediabetes. This is particularly important given current debates around the use of pharmaceutical drugs to treat prediabetes and about whether prediabetes should be diagnosed and treated.

EVIDENCE ACQUISITION

Data Sources and Searches

MEDLINE, Embase, and Cochrane Library databases were searched systematically for articles published from January 1, 2000 to June 27, 2018. Investigators used combinations of Medical Subject Headings and search terms such as *prediabetes*, *prevention*, *regression*, and *risk reduction* (an example of a full search string is presented in Appendix Table 1). Relevant published meta-analyses were also reviewed to identify additional studies to include. The review protocol was registered in PROSPERO (CRD42017067750) and the

present report adheres to PRISMA guidelines for reporting systematic reviews incorporating network meta-analyses of healthcare interventions.²¹

Study Selection

Eligible studies were those conducted among adults with prediabetes, testing any non-surgical intervention aimed to prevent diabetes or improve glucose regulation, lasting 3 months, using a randomized controlled design with any comparison group (i.e., control or lower intensity/alternative intervention), and reporting achievement of normoglycemia as an outcome. Prediabetes was defined according to the American Diabetes Association or World Health Organization criteria as follows^{22,23}: fasting blood glucose level of 5.6–7.0 mmol/L or 6.1–7.0 mmol/L, a 2-hour post 75-mg oral glucose tolerance test (OGTT) plasma blood glucose level of 7.8–11.0 mmol/L, or hemoglobin A1c measure of 5.7%–6.4%. Studies testing surgeries; studies conducted in individuals with gestational diabetes, type 1 diabetes, children, or with other chronic diseases (e.g., women with polycystic ovary syndrome, men with HIV); and animal studies were excluded. Two reviewers independently screened study abstracts and full texts; discrepancies on inclusion decisions were resolved through discussions. Reviewers were not masked to author or journal names during this process.

Data Extraction and Risk of Bias Assessment

A standardized electronic fillable data form was designed to extract the data of interest. Two reviewers conducted the data extraction for all studies. A third reviewer conducted a second data extraction among 20% of the studies to detect and correct any data entry errors. For the primary outcome, the number of participants with prediabetes who achieved normal blood glucose levels by the end of the active intervention period was extracted. Reversion to normal glucose levels was defined as achieving fasting blood glucose levels of <5.6 or <6.1 mmol/L, OGTT plasma blood glucose levels of <7.8 mmol/L, or hemoglobin A1c <5.7% at the end of the intervention. Additional information extracted included treatment tested (e.g., medication type, dose), study characteristics (e.g., country, duration), and participant characteristics (e.g., age, sex, baseline BMI, race). For studies that did not report the data of interest, corresponding authors were contacted to request the information.

Risk of bias in individual studies was assessed by 3 independent reviewers, with discrepancies resolved through discussions. The Cochrane Collaboration tool was used,²⁴ which assesses the risk of bias in a study based on 7 domains: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other bias. For each domain, studies were categorized as having low, high, or unclear risk of bias based on established criteria outlined in the tool. High risk of bias in a domain was interpreted as plausible bias that seriously weakens confidence in the results; low risk of bias was plausible bias unlikely to seriously weaken confidence in the results; and unclear risk of bias indicated there was insufficient information to issue a judgment. For this review, overall study risk of bias was categorized as follows: low when 5 domains were deemed as low risk and high when 2 domains were deemed as high or unclear.

Data Synthesis and Analyses

For analyses, duplicate reports from the same study were excluded, and only the report with the most relevant and complete data was used. In studies testing different doses or combinations of the same treatments, the arm with the most intensive intervention/dose was included (e.g., longer intervention duration, higher medication dose). Data from published articles were obtained in 2018. The initial data analysis was conducted in 2019 and updated in 2021.

To obtain pooled effects for the various interventions in 1 parsimonious model, an arm-based network meta-analysis was conducted.²⁵ For this, all study arms were first divided into intervention and control arms: Intervention arms were those receiving any intervention or treatment, whereas control arms received no intervention or placebo. Placebo or control arms that received a lifestyle modification intervention were categorized as lifestyle intervention arms. After this, arms from all studies were grouped according to the specific intervention/medication tested and the geometry of the network was summarized graphically in a network plot.

The pooled relative risk (RR) and the risk difference (RD) between intervention and control, as well as between treatments, were estimated using a random-effects frequentist model weighted by the inverse variance. A multivariate mixed model approach was used to account for the correlations in multi-arm studies.²⁶ The number needed to treat was computed as $1 \div \text{RD}$ for each intervention/treatment. Between-study heterogeneity for treatment effects was assessed using the I^2 statistic and the p -value for heterogeneity (via the Cochrane's Q test). An I^2 value $\geq 75\%$ or a p -value < 0.05 was considered high between-study heterogeneity.²⁷ Publication bias was assessed via Egger's test and considered present if the test was significant ($p < 0.05$).

Subgroup analyses according to participant sex, age, race, BMI, weight loss percentage, and normoglycemia ascertainment (e.g., based on fasting glucose vs. or glucose tolerance) were conducted to explore sources of heterogeneity in treatment effects. Consistency between direct and indirect estimates was assessed via node splitting, where network estimates were split into the contribution of direct and indirect evidence to identify inconsistency in specific treatment comparisons in the network. Finally, a sensitivity analysis was conducted to isolate the treatment effects among studies with low risk of bias. The analyses described were conducted using the Netmeta package²⁸ in R, version 1.2–1. An independent statistician ran the analyses described here separately to identify and address potential errors and inconsistencies in the data or analyses.

Strength of the Evidence Assessment

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach for network meta-analysis²⁹ was used to determine the strength of the evidence summarized in the meta-analysis. For this, the strength of the evidence for each treatment was categorized as strong, moderate, low, or very low based on the presence of risk of bias, inconsistency of results, imprecision, publication bias, and magnitude of treatment effects. In this study, the evidence for all treatments was considered strong to start: The evidence

was downgraded by 1 level (e.g., from strong to moderate) if 20%–39% of studies testing a specific intervention/treatment had high risk of bias, or if publication bias was present (Egger's test $p < 0.05$), or if the observed effect heterogeneity was moderate ($I^2 = 50\%–74\%$ according to existing recommendations²⁷). The strength of the evidence was downgraded by 2 levels (e.g., from strong to low) if 40% of studies testing a treatment had high risk of bias, if the observed effect heterogeneity was high ($I^2 \geq 75\%$ ²⁷), or if the 95% confidence intervals for the effect estimate were wide.

EVIDENCE SYNTHESIS

Systematic Review

Of 3,547 identified titles, 54 articles met the inclusion criteria and were included in the systematic review (Appendix Figure 1). Participant and intervention characteristics across the 54 studies are presented in Appendix Table 2. The 54 studies enrolled 35,289 participants with a mean age of 53 years, 39% of participants were male, and 30% of participants were White/European. Prediabetes was identified using fasting blood glucose in 2 studies, OGTT in 19 studies, and a combination of fasting blood glucose, OGTT, or hemoglobin A1c in 33 studies. Seventeen studies used the American Diabetes Association diagnostic criteria, 24 used the World Health Organization diagnostic criteria, and 6 did not report the criteria used. Most of the studies (41%) were conducted in Asia, 31% in North America, 15% in Europe, 11% across multiple countries, and 2% in Oceania.

Regarding risk of bias, the assessment showed most studies reported how the random sequence was generated ($n=25$), how blinding of participants was conducted ($n=26$), and how group allocation was concealed ($n=18$), granting them low risk of bias in these domains. Blinding of outcome assessors was explicitly reported in 8 studies and not reported in the rest of the studies. However, the authors concluded this did not affect glucose outcome assessment and assigned a low risk of bias for this domain to all 54 studies. No significant protocol deviations were found across 54 studies, and 49 had low percentage of missing data (Appendix Figure 2). Based on the criteria set for this study, 40 studies were considered to have low risk and 14 studies to have high risk of bias.

Meta-Analysis

Of the 54 studies identified in the systematic review, 6 were additional reports of trials already included and 1 study did not provide sufficient data for the meta-analysis. The remaining 47 studies were included in the meta-analysis ($n=26,460$, mean age=53 years, 46% male, 31% White, mean BMI=30 kg/m²). These studies contributed 67 intervention arms (including placebo or control arms that received a lifestyle modification intervention) and 35 control/placebo arms. Intervention and control/placebo arms were balanced in demographic and clinical characteristics at baseline (Table 1).

Of the intervention arms, 27 tested lifestyle modification strategies (through dietary or physical activity/exercise improvements), 25 medications, 5 dietary supplements (vitamin D, magnesium, and L-arginine), and 10 Chinese medicine. Medications tested included insulin sensitizers (metformin, rosiglitazone, and pioglitazone), insulin secretagogues (glipizide),

AGIs (acarbose and voglibose), dipeptidyl peptidase 4 inhibitors (linagliptin), glucagon-like peptide 1 receptor agonists ([GLP-1]; liraglutide, dapagliflozin, and exenatide), fenofibrate, renin–angiotensin system blockers (ramipril), and a lipase inhibitor (orlistat). Figure 1 shows the asymmetrical network plot where lifestyle modification (27 arms, $n=4,065$) and insulin sensitizers (13 arms, $n=4,342$) were the most tested approaches against control/placebo arms.

Meta-analytic estimates for the different treatments are presented in Table 2 and Figure 2. Groups receiving GLP-1 were more likely to achieve normoglycemia than control groups after a median follow-up of 1.7 years (68% vs 21%; RD=0.47, 95% CI=0.22, 0.72; RR=3.53, 95% CI=1.69, 7.37; NTT=2). Individuals in the lipase inhibitor group were more likely to achieve normoglycemia than control after a median follow-up of 1.6 years (61% vs 21%; RD=0.40, 95% CI=0.04, 0.76; RR=2.57, 95% CI=1.14, 5.81; NTT=3). Individuals in the fenofibrate group were more likely to achieve normoglycemia than control after a median follow-up of 0.5 years (58% vs 21%; RD=0.37, 95% CI=0.02, 0.71; RR=1.85, 95% CI=0.82, 4.19; NTT=3). Groups receiving AGIs were more likely to achieve normoglycemia than control after a median follow-up of 2.7 years (50% vs 21%; RD=0.29, 95% CI=0.14, 0.43; RR=2.01, 95% CI=1.40, 2.91; NTT=4). Those receiving insulin sensitizer agents were also more likely to achieve normoglycemia than control after a median follow-up of 2.0 years (44% vs 21%; RD=0.23, 95% CI=0.14, 0.33; RR=1.62, 95% CI=1.23, 2.14; NTT=4).

Regarding non-pharmacological interventions, individuals receiving magnesium supplements were more likely to achieve normoglycemia than control (65% vs 21%; RD=0.44, 95% CI=0.10, 0.78; RR=7.25, 95% CI=2.15, 24.43; NTT=2) at a median follow-up of 0.3 years. Chinese medicine groups were also more likely to achieve normoglycemia than control at a median follow-up of 1 year (52% vs 21%; RD=0.31, 95% CI= 0.19, 0.42; RR=2.66, 95% CI=1.93, 3.68; NTT=3). Finally, lifestyle modification groups were more likely to achieve normoglycemia than control at a median follow-up of 1.6 years (39% vs 21%; RD=0.18, 95% CI=0.10, 0.25; RR=1.76, 95% CI=1.41, 2.19; NTT=6).

The full network meta-analysis showed some treatments achieved higher normoglycemia levels relative to other treatments (Table 2). Specifically, the GLP-1 group was more likely to achieve normoglycemia than renin–angiotensin system blockade medication (RD= −0.43, 95% CI= −0.83, −0.03), vitamin D (RD= −0.38, 95% CI= −0.69, −0.06), and lifestyle modification groups (RD= −0.30, 95% CI= −0.54, −0.05). Similarly, Chinese medicine groups were more likely to achieve normoglycemia than lifestyle modification groups (RD= −0.13, 95% CI= −0.24, −0.02). No other significant between-treatment differences were observed. Effect estimates in the full network model were heterogeneous for both RR ($I^2=82.7\%$, 95% CI=77.4%, 86.7%) and RD ($I^2=91\%$, 95% CI=88.8%, 92.8%).

Consistency and Strength of the Evidence Assessment

Subgroup analyses comparing intervention versus control arms showed effect estimates varied according to clinical and study characteristics (Appendix Table 3). Specifically, AGIs (RD=0.24, 95% CI=0.11, 0.38), Chinese medicine (RD=0.27, 95% CI=0.13, 0.41), and lifestyle modification approaches (RD=0.15, 95% CI=0.07, 0.24) had beneficial effects in studies where participants were aged ≥ 50 years, but null effects were observed in studies

where participants were aged <50 years. AGIs were beneficial in studies where <80% of participants were White (RD=0.35, 95% CI=0.18, 0.53) and in studies where mean BMI was <30 kg/m² (RD=0.35, 95% CI=0.19, 0.52), but no effects were observed in studies where 80% of participants were White (RD=0.04, 95% CI= -0.13, 0.21) and where mean BMI was 30 kg/m² (RD=0.04, 95% CI= -0.25, 0.34).

Lifestyle modification approaches had beneficial effects in studies where impaired glucose tolerance or impaired fasting glucose were used to determine normoglycemia achievement (RD=0.21, 95% CI=0.08, 0.33), whereas no effects were observed in studies where only impaired glucose tolerance was used (RD=0.10, 95% CI= -0.04, 0.24). AGIs and insulin sensitizers had a beneficial effect among participants who lost ≥4% of their baseline weight (RD=0.55, 95% CI=0.25, 0.86 and RD=0.43, 95% CI=0.21, 0.66, respectively), whereas null effects were observed among participants that lost <4% (RD=0.04, 95% CI= -0.22, 0.31 and RD=0.10, 95% CI= -0.02, 0.23, respectively). Finally, shorter duration studies (<12 months) had larger effect sizes than longer duration studies (>12 months), reaching 2 times higher normoglycemia estimates for all treatments (Appendix Table 3).

Sensitivity analyses including only 34 studies that were deemed to have low risk of bias yielded similar normoglycemia estimates to those obtained in analyses including all studies (Appendix Table 4). Regarding consistency, estimates from direct and indirect evidence were consistent (i.e., in the same direction) for most treatments (Appendix Figure 3). The main discrepancy was found in the AGI versus lifestyle modification comparison, with direct evidence from head-to-head studies showing AGIs were superior to lifestyle (RD=0.25, 95% CI=0.04, 0.46), and indirect evidence showing no difference (RD= -0.04, 95% CI= -0.25, 0.17).

Using the GRADE assessment, 33% of studies testing lifestyle modification approaches had high risk of bias due to lack of blinding to intervention. However, this was judged as not placing a major influence on the primary outcome. Given that no other GRADE criteria were of concern, the strength of the evidence for lifestyle modification was deemed strong. For studies testing insulin sensitizers, AGIs, and GLP-1, the strength of the evidence was deemed as moderate. This was due to the high heterogeneity in treatment effects observed in studies testing these treatments (I^2 =60%–85%), the fact that 33% of AGI studies and 40% of insulin sensitizer studies were at high risk of bias, and due to the imprecision in the GLP-1 effect estimate (there were only 2 studies). The strength of the evidence for Chinese medicine was deemed as low because 30% of studies had high risk of bias, the effect estimate was imprecise, and publication bias was present (Egger's test p <0.001). Finally, the strength of the evidence for fenofibrate, the lipase inhibitor, and the magnesium supplement was deemed very low because the effect estimates were imprecise and there was a single study testing each treatment that had high risk of bias. The full GRADE assessment for all treatments is presented in Appendix Table 5.

DISCUSSION

This systematic review and meta-analysis of RCTs compared the effectiveness of diverse interventions for reversing prediabetes. It found that non-pharmacological approaches

(lifestyle modification, Chinese medicine, and magnesium supplementation) as well as pharmacological approaches (GLP-1, AGIs, insulin sensitizers, lipase inhibitors, and fenofibrate) can reverse prediabetes. The achieved normoglycemia levels were larger for pharmacological interventions (23%–47%) than for non-pharmacological approaches (18%–44%). However, considering the risk of bias, precision, heterogeneity, and publication bias present in the included studies,²⁹ the strength of the evidence is strongest for lifestyle modification, moderate for pharmacological agents, and low or very low for the remaining approaches. Based on these findings, and in line with current expert recommendations,³⁰ lifestyle modification should be the first-line approach for treating prediabetes.

Groups receiving lifestyle modification interventions were 18% more likely to achieve normal glucose levels than control groups, with 6 people needing the intervention for one to reverse to normal. A previous meta-analysis of 6 studies showed that improvements in dietary and physical activity behaviors were associated with 53% higher RR for reversing to normal glucose levels among people with prediabetes,¹⁴ which aligns with the RR observed in this study. In this meta-analysis, lifestyle modification was most beneficial in studies where participants were aged >50 years, suggesting this age group may experience the greatest benefits. Studies where only OGTT was used to determine prediabetes reversion did not achieve significant reversion levels; however, this may be explained by the fact that most lifestyle modification approaches using OGTT were compared against other treatments (e.g., a drug or a Chinese medicine) as opposed to a control condition. As the strength of the evidence for lifestyle modification studies is the strongest,²⁹ these findings support current expert statements³⁰ recommending lifestyle modification as the first-line approach for treating prediabetes.

Regarding pharmacological interventions, GLP-1 receptor agonists achieved 47%, AGIs achieved 29%, and insulin sensitizers (metformin, rosiglitazone, and pioglitazone) achieved 23% higher reversion estimates than control groups. To get 1 person with prediabetes to reverse to normal glucose levels, 2, 4, and 4 people would need treatment, respectively. These findings align with previous estimates showing AGIs and insulin sensitizers are associated with 2 times higher normoglycemia odds than control groups.¹³ Subgroup analyses suggest AGIs may be more beneficial in older age groups (>50 years), people without obesity (BMI <30 kg/m²), and among more racially diverse populations (<80% White). Additionally, the effect of AGIs and insulin sensitizers seems to be mediated by weight loss given only those who lost ≥4% of their baseline body weight experienced benefits. As the strength of the evidence was moderate for these medications and regulatory agencies have not approved medications for treating prediabetes, these drugs should not be used for this purpose.

Although this study found Chinese medicine, a lipase inhibitor (orlistat), fenofibrate, and a magnesium supplement were associated with higher normoglycemia levels than control groups, the strength of the evidence was low or very low for these approaches. Studies focused on rigorously examining the effects of these approaches on prediabetes reversion are lacking; aside from Chinese medicine, only 1 study per treatment was included in this meta-analysis. Evidence is more prominent for Chinese medicine, which has led to meta-analyses examining the effects of this approach on prediabetes reversal¹¹ and potential

mechanisms of action.³¹ Evidence on magnesium supplementation for reversing prediabetes may emerge in the near future.³² Overall, there is no sufficient evidence, neither support from expert recommendations, or approval from regulatory agencies to use these approaches for treating prediabetes.

Because the literature search was completed on June 27 of 2018, potentially eligible studies published after this date were not included. To determine whether the present analysis needed updating, the authors conducted a new search from this date up to August 20, 2021. They found 194 new study titles, of which 47 abstracts were screened, and 8 studies met the eligibility criteria. Of these, 4 studies tested lifestyle modification approaches (diet and physical activity strategies): 3 studies found 8%–25% higher normoglycemia levels in intervention compared with control groups,^{33–35} and 1 found no difference.³⁶ Two studies tested medications: lorcaserin (serotonin receptor agonist) which was associated with a non-significant increase in normoglycemia among 185 patients with prediabetes,³⁷ and saxagliptin (dipeptidyl peptidase 4 inhibitor), which promoted reversion to normal glucose tolerance in 11 of 12 patients receiving it.³⁸ The remaining 2 studies tested vitamin D supplementation among 121 Asian Indian women,³⁹ and *Gymnema sylvestre* (a plant from India) among 30 patients.⁴⁰ Compared with control groups, more participants in the vitamin D (51% vs 44%) and *Gymnema sylvestre* group (47% vs 0%) returned to normal glucose levels. Because these studies are not likely to change the results, the authors decided not to update the present analyses.

One final point is the fact that 21% of control participants reversed to normal glucose levels in the meta-analysis; this falls within previous estimates indicating that 17%–42% people with prediabetes reverse to normal glucose levels within 11 years.⁴¹ Though some individuals with prediabetes reverse to normal without intervention, those who remain in the prediabetes state have increased risk for developing cardiovascular and renal diseases, even if they do not develop diabetes.^{4–6} Hence, working toward reversing prediabetes is a worthwhile approach for lowering cardiometabolic risk, as supported by long-term evidence from RCTs.^{16,18–20} Although there is a debate about whether a prediabetes diagnosis should be used,⁴² this meta-analysis supports expert statements recommending identification and treatment of this condition.^{2,30} However, the authors recognize that, unlike with diabetes remission, there is no consensus definition on what prediabetes remission, reversal, or normal glucose regulation restoration might constitute, which warrants further attention.⁴³

Limitations

These findings should be interpreted considering some limitations. There was heterogeneity in study characteristics and effect estimates, which was partially explained in subgroup analyses. Twelve percent of the studies had high risk of bias; however, in sensitivity analyses excluding these studies, neither effect estimates nor study conclusions changed. There was inconsistency between direct and indirect evidence in the AGI versus lifestyle modification comparisons; hence, indirect comparisons between these treatments should be interpreted with caution. Few medication studies reported results after a washout period: this prevented the investigators from assessing whether the effect of these medication persisted after withdrawal. Finally, the search terms employed for the systematic review were in English

and it is possible that studies published in other languages (e.g., Spanish) may have been missed.

CONCLUSIONS

This systematic review and meta-analysis of RCTs identified a range of pharmacological and non-pharmacological strategies that can reverse prediabetes. However, only lifestyle modification interventions provide strong evidence of effectiveness, which supports current expert statements recommending this as the first-line approach for treating prediabetes. To date, neither medications nor alternative approaches are recommended in expert statements or have been approved by regulatory authorities for treating prediabetes—the present findings support these conclusions. Findings from this study can motivate preventive medicine professionals to introduce lifestyle modification approaches in their clinical practice to treat prediabetes. Treating prediabetes could potentially offset, or at least delay, future medication needs and economic costs to individuals and the payer systems where they live. With close to 400 million people living with prediabetes worldwide, the potential of reversing this condition is significant.

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Appendix

Appendix

Appendix Table 1.

Search String Used for PubMed Search

1. Prediabetes terms (results=48,541)	"prediabetic state"[MeSH] OR prediabetic OR prediabetes OR pre-diabetic OR pre-diabetes OR "glucose intolerance"[MeSH] OR impaired fasting glucose OR impaired glucose tolerance
2. Normoglycemia terms (results=242,248)	normoglycemic OR normoglycemia OR normoglycaemic OR normoglycemia OR normal glucose tolerance OR normal fasting glucose OR "hypoglycemic agents"[MeSH] OR "hypoglycemic agents"
3. Outcomes (results=6,498,412)	Treatment outcome OR remission OR reverse OR reduction OR reversal OR risk reduction OR risk OR regulation OR prevention
4. 1 AND 2 AND 3 (results 9,373 humans and animals)	((("prediabetic state"[MeSH] OR prediabetic OR prediabetes OR pre-diabetic OR pre-diabetes OR "glucose intolerance"[MeSH] OR impaired fasting glucose OR impaired glucose tolerance))) AND (((normoglycemic OR normoglycemia OR normoglycaemic OR normoglycemia OR normal glucose tolerance OR normal fasting glucose OR "hypoglycemic agents"[MeSH] OR "hypoglycemic agent*")))) AND (Treatment outcome OR remission OR reverse OR reduction OR reversal OR risk reduction OR risk OR regulation OR prevention)
5. Limit 4 to animals (results 2,362)	((("prediabetic state"[MeSH] OR prediabetic OR prediabetes OR pre-diabetic OR pre-diabetes OR "glucose intolerance"[MeSH] OR impaired fasting glucose OR impaired glucose tolerance))) AND (((normoglycemic OR normoglycemia OR normoglycaemic OR normoglycemia OR normal glucose tolerance OR normal fasting glucose OR "hypoglycemic agents"[MeSH] OR "hypoglycemic agent*")))) AND (Treatment

6. #4 NOT #5
AND date from 2001+
(Results=5,503)

outcome OR remission OR reverse OR reduction OR reversal OR risk reduction OR risk OR regulation OR prevention) Filters: Other Animals

(((((“prediabetic state”[MeSH] OR prediabetic OR prediabetes OR pre-diabetic OR pre-diabetes OR “glucose intolerance”[MeSH] OR impaired fasting glucose OR impaired glucose tolerance)) AND (normoglycemic OR normoglycemia OR normoglycaemic OR normoglycemia OR normal glucose tolerance OR normal fasting glucose OR “hypoglycemic agents”[MeSH] OR “hypoglycemic agents”)) AND (Treatment outcome OR remission OR reverse OR reduction OR reversal OR risk reduction OR risk OR regulation OR prevention))) NOT ((((((“prediabetic state”[MeSH] OR prediabetic OR prediabetes OR pre-diabetic OR pre-diabetes OR “glucose intolerance”[MeSH] OR impaired fasting glucose OR impaired glucose tolerance)) AND (normoglycemic OR normoglycaemic OR normoglycemia OR normal glucose tolerance OR normal fasting glucose OR “hypoglycemic agents”[MeSH] OR “hypoglycemic agents”)) AND (Treatment outcome OR remission OR reverse OR reduction OR reversal OR risk reduction OR risk OR regulation OR prevention)) AND Animals[Mesh:noexp]) AND (“2001/01/01”[PDat] : “2030/12/31”[PDat]))

Appendix Table 2.

Baseline Participant and Intervention Characteristics for Each Study Included in the Systematic Review and Meta-Analysis

Included only in Systematic Review (n=9)								
Author (year) Country	Participant characteristics					Intervention characteristics		
	Age (years)	N	Male	Race	BMI (kg/m ²)	Mean Follow up (years)	Treatment tested	Dose
DeFronzo (2013) ¹ U.S.	53	213	42%	50% White	33.0	2.4 (median)	Insulin Sensitizers (Pioglitazone)	30–45 mg per day for 2 years
Rosenstock (2010) ² U.S.	4	73	18%	NR	39.6	NR	GLP-1 (Exenatide) plus diet	10 ug 2 times per day with a 5 ug dose initiation period and caloric reduction in diet for all meals for 24 weeks
Perreault (2009a) ³ U.S.	50	850	35%	54% White	33.0	NR	Lifestyle modification	16 individual, 1-hour counseling sessions focused on increasing physical activity up to 150 minutes of moderate to vigorous intensity physical activity per week, delivered over 1 year
Perreault (2009b) ³ U.S.	51	832	36%	57% White	33.0	NR	Insulin sensitizers (Metformin)	850 mg 2 times per day delivered over 1 year
Perreault (2012a) ⁴ U.S.	NR	736	35%	53% White	33.0	5.4	Lifestyle modification	16–20 individual counseling sessions per year focused on increasing physical activity up to 150 minutes of moderate to vigorous intensity physical activity per week (participants could choose to do a minimum of 16 sessions and maximum of 20 sessions) for 1 year

Included only in Systematic Review (n=9)								
Participant characteristics						Intervention characteristics		
Author (year) Country	Age (years)	N	Male	Race	BMI (kg/ m ²)	Mean Follow up (years)	Treatment tested	Dose
Perreault (2012b) ⁴ U.S.	NR	647	31%	60% White	33.0	5.4	Insulin sensitizer (Metformin)	850 mg 2 times per day for 1 year
Snehalatha (2009) ⁵ India	NR	321	NR	100% White	25.5	3.0	Insulin sensitizer (Metformin) plus lifestyle modification	500 g per day and advice on physical activity and diet for 3 years
Tripathy (2014) ⁶ U.S.	54	207	45%	NR	33.4	2.4	Insulin sensitizer (Pioglitazone)	30 mg per day for 1 month and then 45 mg per day for 23 months
Tripathy (2016) ⁷ U.S.	54	152	NR	NR	33.4	2.4	Insulin sensitizer (Pioglitazone)	30 mg per day for a year
Included in Systematic Review and Meta-Analysis (n=47)								
Author (year) Country	Age (years)	N	Male	Race	BMI (kg/ m ²)	Mean follow up (years)	Treatment tested	Dose
Barengolts (2015) ⁸ U.S.	58.2	87	100%	100% Black	32.4	1.0	Vitamin D	50,000 IU per week
Bennett (2004) ⁹ Multiple countries	62.7	9	56%	NR	30.2	0.23	Insulin Sensitizer (Rosiglitazone)	4 mg per day for 12 weeks
Bhopal (2014) ¹⁰ Scotland	52.8	85	46%	100% Asian	30.6	3.0	Lifestyle Modification	15 visits from a dietician focused on weight loss over 3 years
Block (2015) ¹¹ U.S.	55.0	163	68%	67% White	31.1	0.5	Lifestyle Modification	Weekly emails with tailored behavior change support for 6 months
Chiasson (2002) ¹² Multiple countries	54.3	682	48%	97% White	31.0	3.3	AGI (Acarbose) plus Lifestyle Modification	100 mg at 3 times per day for 3 years
DeFonzo (2011) ¹³ U.S.	53.0	303	42%	51% White	33.0	2.4	Insulin Sensitizer (Pioglitazone)	30 mg per day for first month. Then, 45 mg per day for remaining 23 months
DPP Research Group (2002a) ¹⁴ U.S.	50.9	1,073	34%	56% White	33.9	2.8	Insulin Sensitizer (Metformin)	850 mg at 2 times per day for 24 weeks
DPP Research Group (2002b) ¹⁴ U.S.	50.6	1,079	32%	54% White	33.9	2.8	Lifestyle Modification	One-year lifestyle modification program including 2 phases: (1) an intensive 4- month phase of 16 individual counselling sessions focused on improving physical

Included only in Systematic Review (n=9)									
Participant characteristics						Intervention characteristics			
Author (year) Country	Age (years)	N	Male	Race	BMI (kg/ m ²)	Mean Follow up (years)	Treatment tested	Dose	
								activity and dietary behaviors and (2) a maintenance phase including monthly individual counseling sessions delivered over 24 weeks	
DREAM (2006) ¹⁵ Multiple countries	54.6	2,635	42%	NR	30.8	3 (median)	Insulin Sensitizer (Rosiglitazone)	8 mg per day for 3 years	
DREAM (2006) ¹⁶ Multiple countries	54.7	2,623	40%	NR	30.9	3 (median)	Insulin Sensitizer (Rampiril)	5 mg per day for first 2 months 10 mg per day for next 10 months 15 mg per day until end of study (up to 3 years)	
Dutta (2014a) ¹⁷ India	48.4	68	43%	NR	26.3	2.4	Vitamin D plus Lifestyle Modification	60,000 IU per week, 1,250 mg Calcium per month, and diet and physical activity	
Dutta (2014b) ¹⁷ India	47.4	57	31%	NR	26.8	2.4	Lifestyle Modification	1,250 mg Calcium per month and diet and physical activity	
Eriksson (2006) ¹⁸ Finland	53.0	17	11%	NR	27.9	3.2	Insulin Secretagogue (Glipizide)	2.5 mg per day for 6 months	
Fan (2004a) ¹⁹ China	54.6	23	43%	100% Asian	25.8	NR	Chinese Medicine	Jiangtang Bushen Recipe at 2–3 administrations per week for 1 year	
Fan (2004b) ¹⁹ China	57.0	22	50%	100% Asian	26.0	NR	Lifestyle Modification	Guided aerobic exercise at 1 time per day for 30–60 minutes each session for 1 year	
Fang (2004a) ²⁰ China	55.0	36	53%	100% Asian	25.3	NR	Lifestyle Modification	NR	
Fang (2004b) ²⁰ China	50.0	45	56%	100% Asian	24.9	NR	AGI (Acarbose)	NR	
Fang (2004c) ²⁰ China	50.0	44	54%	100% Asian	25.2	NR	Insulin sensitizer (Flumamine)	NR	
Fang (2014a) ²¹ China	55.0	223	53%	100% Asian	25.3	1.0	Chinese medicine plus Lifestyle Modification	8.8 g ShenZhu TiaoPi granules at 2 times per day and dietary advice for 1 year	
Fang (2014b) ²¹ China	54.6	216	55%	100% Asian	25.3	1.0	Lifestyle Modification	Dietary advice for 1 year	
Gaddam (2015) ²² India	NR	52	NR	100% Asian	26.2	3.0	Chinese medicine	Fenugreek 5 g powder 2 times per day for 3 years	

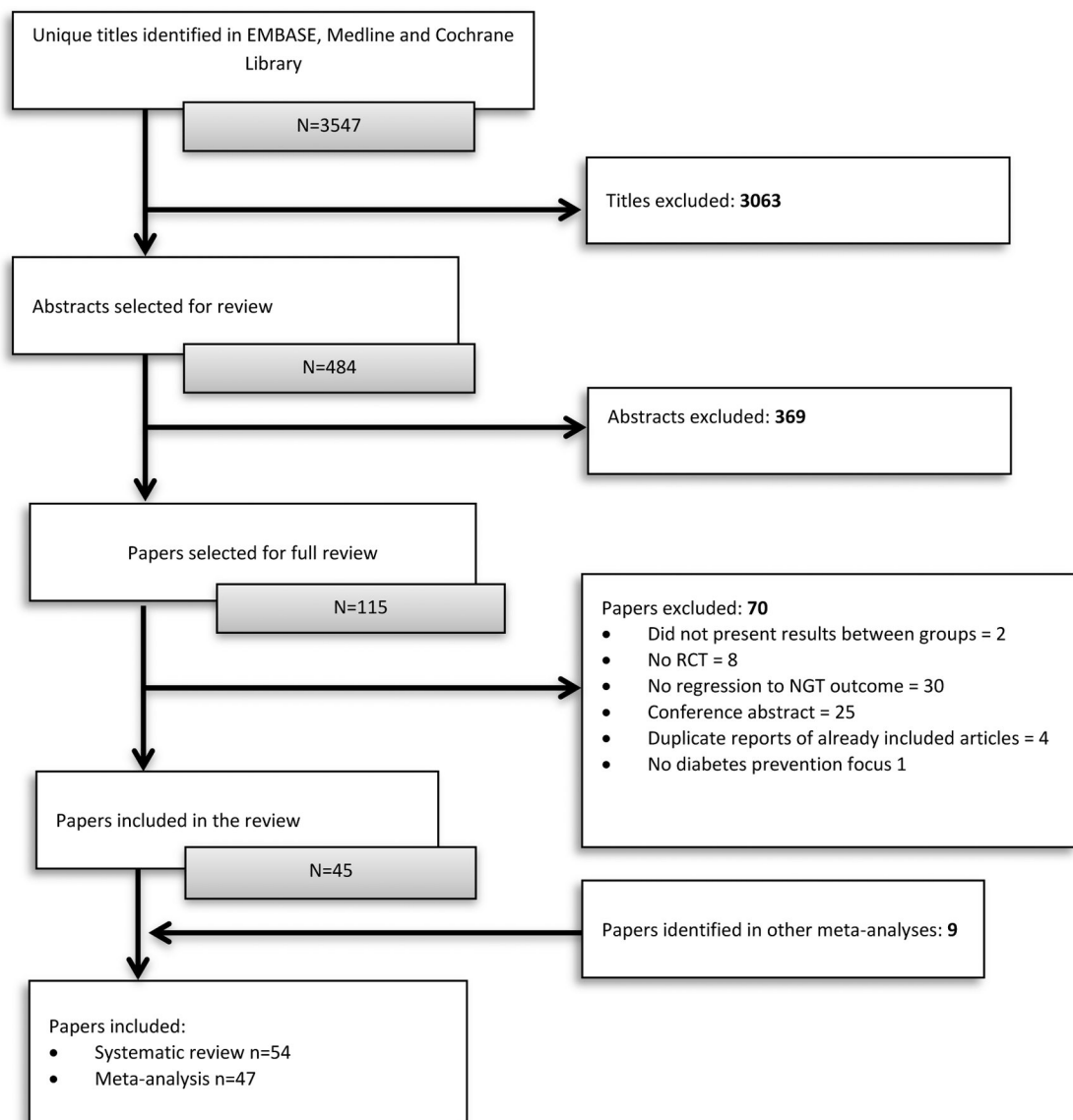
Included only in Systematic Review (n=9)									
Participant characteristics						Intervention characteristics			
Author (year) Country	Age (years)	N	Male	Race	BMI (kg/ m ²)	Mean Follow up (years)	Treatment tested	Dose	
Gagnon (2011) ²³ Canada	54.8	22	55%	100% White	34.1	1.0	Lifestyle Modification	25 seminars about diet, exercise, and behavior change over 1 year	
Gao (2013) ²⁴ China	49.3	230	43%	100% Asian	25.1	3.0	Chinese Medicine	Tangzhiping granules 5g at 2 times per day	
Gonzalez- Heredia (2017a) ²⁵ Mexico	51.9	8	37%	100% Latin	31.2	0.23	Insulin Sensitizer (Metformin)	500 mg per day for 3 months	
Gonzalez- Heredia (2017b) ²⁵ Mexico	49.3	8	37%	100% Latin	31.3	0.23	DPP-4 (Linagliptin)	5 mg per day for 3 months	
Guerrero- Romero (2015) ²⁶ Mexico	42.5	59	42%	100% Latin	30.6	0.23	Magnesium	30 mL bolus per day for 4 months	
Heymsfield (2000) ²⁷ Multiple countries	43.9	67	19%	88% White	35.6	1.6	Lipase inhibitor (Orlistat)	120 mg 3 times per day for 108 weeks	
Heymsfield (2000) ²⁷ Multiple countries	44.3	53	18%	88% White	36.0	1.6	Lifestyle Modification	Individualized diet plan for 108 weeks	
Huang (2016a) ²⁸ China	52.0	60	52%	100% Asian	NR	2.1	Chinese Medicine plus Lifestyle Modification	Tangyiping Granules 10 g at w times per day	
Huang (2016b) ²⁸ China	51.1	60	58%	100% Asian	NR	2.1	Lifestyle Modification	Diet and physical activity modification for 12 weeks	
Jorde (2016) ²⁹ Norway	62.3	256	63%	100% White	30.1	NR	Vitamin D	20,000 IU per week for 5 years	
Kawamori (2009) ³⁰ Japan	55.7	897	60%	100% Asian	25.8	0.9	AGI (Voglibose)	Dose not reported	
Ke (2012a) ³¹ China	46.5	43	51%	100% Asian	28.7	0.5	Chinese Medicine	Modified Linggui Zhugan decoction 2 times per day for 6 months	
Ke (2012b) ³¹ China	45.7	38	67%	100% Asian	28.5	0.5	Lifestyle Modification	Daily, low-calorie diet for 6 months	
Kosaka (2012) ³² Japan	NR	356	100%	100% Asian	24.0	4.0	Lifestyle Modification	Tailored, individualized lifestyle change program over 4 years	
Le Roux (2017) ³³ Multiple countries	47.5	1,505	24%	83% White	38.8	2.8	GLP-1 (liraglutide)	3 mg per day for up to 160 weeks	

Included only in Systematic Review (n=9)								
Participant characteristics					Intervention characteristics			
Author (year) Country	Age (years)	N	Male	Race	BMI (kg/ m ²)	Mean Follow up (years)	Treatment tested	Dose
Lehtovirta (2001) ³⁴ Finland	57.3	20	70%	NR	29.8	0.5	Insulin Sensitizer (Metformin)	500 mg 2 times per day for 6 months
Lian (2014a) ³⁵ China	53.0	198	47%	100% Asian	25.2	1.0	Chinese Medicine plus Lifestyle Modification	1.6 g of Tianqi at 3 times per day and individualized dietary counseling for 12 months
Lian (2014b) ³⁵ China	51.9	191	50%	100% Asian	25.5	1.0	Lifestyle Modification	Individualized dietary counseling for 12 months
Lu (2011a) ³⁶ China	62.4	46	53%	100% Asian	27.1	2.0	Insulin Sensitizer (Metformin)	0.25 g 3 times per day for 2 years
Lu (2011b) ³⁶ China	62.4	49	53%	100% Asian	27.1	2.0	AGI (Acarbose)	50 mg 3 times per day for 2 years
Lu (2011c) ³⁶ China	64.7	86	53%	100% Asian	26.9	2.0	Lifestyle Modification	Educational sessions on diet and physical activity every month for 2 years
Lundkvist (2016) ³⁷ Sweden	53.5	16	40%	100% White	35.8	0.5	GLP-1 (Dapagliflozin and Exenatide)	10 mg per day dapagliflozin and 2 mg per week of exenatide for up to 24 weeks
Monti (2012) ³⁸ Italy	57.2	66	58%	100% White	30.4	2.5	L-arginine	3.2 g at 2 times per day for 1.5 years
Moore (2011) ³⁹ Australia	61.3	183	41%	100% White	29.7	0.5	Lifestyle Modification	Group educational sessions about diet and physical activity once a month for 6 months
O'Brien (2017a) ⁴⁰ U.S.	45.5	30	0	100% Latin	34.4	1.0	Lifestyle Modification	24 sessions on diet and physical activity behavior change over 1 year
O'Brien (2017b) ⁴⁰ U.S.	45.8	27	0	100% Latin	33.2	1.0	Insulin Sensitizer (Metformin)	850 mg at 2 times per day for 1 year
Oldroyd (2006) ⁴¹ UK	58.2	91	46%	100% White	NR	2.0	Lifestyle Modification (Diet and physical activity)	Regular motivational counseling for diet and physical activity over 2 years
Penn (2009) ⁴² UK	56.8	41	41%	100% White	34.1	3.1	Lifestyle Modification (Diet and physical activity)	30-minute session addressing behavioral interventions to change diet and physical activity over 3 years
Ramachandran (2010a) ⁴³ India	NR	125	NR	100% Asian	NR	3.0	Insulin Sensitizer (Metformin)	500 mg per day for 3 years

Included only in Systematic Review (n=9)								
Participant characteristics					Intervention characteristics			
Author (year) Country	Age (years)	N	Male	Race	BMI (kg/ m ²)	Mean Follow up (years)	Treatment tested	Dose
Ramachandran (2010b) ⁴³ India	NR	297	NR	100% Asian	NR	3.0	Lifestyle Modification (Diet and physical activity)	Physical activity and diet recommendations for 3 years
Roman-Ramos (2000) ⁴⁴ Mexico	36.8	15	40%	100% Latin	29.6	0.23	Insulin Sensitizer (Rosiglitazone)	4 mg per day for 12 weeks
Shi (2016) ⁴⁵ China	47.1	32	47%	100% Asian	22.9	0.23	Chinese Medicine	One packet Jinlida granules per day for 12 weeks
Stentz (2016) ⁴⁶ U.S.	43.1	12	25%	83% Black	40.5	0.5	Lifestyle Modification (Diet)	Daily high-protein diets for 6 months
Sun (2015) ⁴⁷ China	55.5	82	51%	100% Asian	NR	2.0	Chinese Medicine plus Lifestyle Modification	Seven JinQi Jiangtang tablets 2 times per day and tailored exercise and diet program for 1 year
Wan (2010a) ⁴⁸ China	NR	20	NR	100% Asian	NR	0.5	Fenofibrate	200 mg per day for 6 months
Wan (2010b) ⁴⁸ China	NR	24	NR	100% Asian	NR	0.5	Insulin Sensitizer (Metformin)	500 mg 3 times per day for 6 months
Wan (2010c) ⁴⁸ China	NR	25	NR	100% Asian	NR	0.5	Lifestyle Modification	Diet plans that included recommendations to limit daily caloric, fat, and energy intake for 6 months
Wang (2000a) ⁴⁹ China	64.0	30	52%	100% Asian	22.7	1.0	AGI (Acarbose)	50 mg at 3 times per day for 12 months
Wang (2000b) ⁴⁹ China	63.0	30	53%	100% Asian	21.0	1.0	Lifestyle Modification	Diet and physical activity recommendations for 12 months
Wei (2008) ⁵⁰ China	51.3	68	44%	100% Asian	NR	0.5	Chinese Medicine	Two packets of Tang No.1 granule at 2 times per day for 6 months
Xu (2013) ⁵¹ China	60.4	41	37%	100% Asian	26.8	1.0	Lifestyle Modification	Daily meal replacement and physical activity coaching for 1 year
Zhou (2011) ⁵² China	57.3	59	19%	100% Asian	NR	0.5	Lifestyle Modification	Diet adjustment and individualized physical activity interventions that involved sports for 6 months
Zinman (2010a) ⁵³ Canada	55.0	103	35%	75% White	31.3	3.9	Insulin Sensitizer (Rosiglitazone and Metformin)	500 mg metformin and 2 mg rosiglitazone at 2 times per day for 1 year

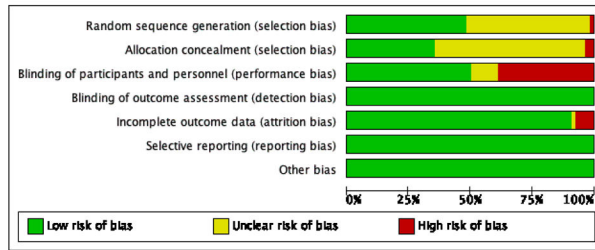
Included only in Systematic Review (n=9)								
Participant characteristics					Intervention characteristics			
Author (year) Country	Age (years)	N	Male	Race	BMI (kg/ m ²)	Mean Follow up (years)	Treatment tested	Dose
Zinman (2010b) ⁵³ Canada	57.3	104	32%	75% White	32.0	3.9	Lifestyle Modification	Five 1-on-1 diet and physical activity modification sessions for 1 year
Zong (2015) ⁵⁴ China	NR	84	54%	100% Asian	26.1	NR	Lifestyle Modification	Intensive nutrition and physical activity guidance

AGI, alpha glucosidase inhibitors; DPP-4, dipeptidyl peptidase 4 inhibitors; GLP-1, glucagon-like peptide 1 receptor agonists; RAS, renin-angiotensin system; NR, not reported.

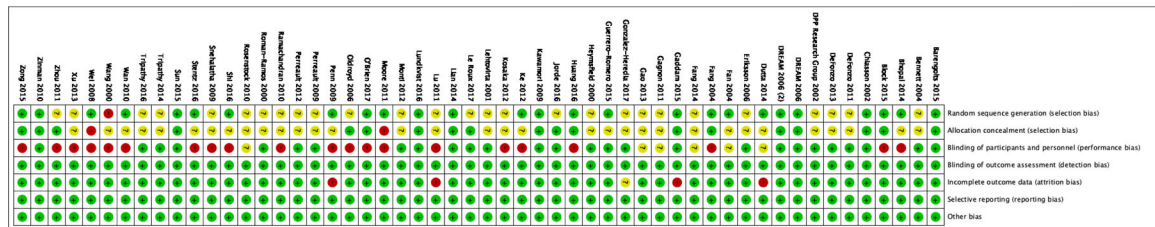


Appendix Figure 1. PRISMA study selection flow chart.

A. Summary for all studies



B. Assessment for each study



Appendix Figure 2. Risk of bias assessment results.

Appendix Table 3.

Subgroup Analyses Exploring Transitivity (i.e., Treatment Effect Heterogeneity) by Participant Characteristics and Study Follow Up

Variable	AGI	Chinese medicine	Insulin sensitizer	Lifestyle modification	Vitamin D
Sex					
<50% Male		0.20 (0.02, 0.39)	0.24 (0.09, 0.38)	0.23 (0.10, 0.36)	0.21 (-0.17, 0.60)
50% Male	—	0.36 (0.22, 0.50)	0.17 (0.01, 0.33)	0.15 (0.07, 0.24)	0.05 (-0.10, 0.20)
Age, years					
<50	0.51 (-0.10, 1.13)	0.39 (-0.03, 0.81)	0.41 (0.02, 0.80)	0.27 (-0.09, 0.64)	0.21 (-0.49, 0.92)
50	0.24 (0.11, 0.38)	0.27 (0.13, 0.41)	0.14 (0.03, 0.25)	0.15 (0.07, 0.24)	0.04 (-0.26, 0.33)
Race					
<80% White	0.35 (0.18, 0.53)		0.24 (0.13, 0.35)	0.18 (0.09, 0.27)	0.12 (-0.13, 0.37)
80% White	0.04 (-0.13, 0.21)	—	0.12 (0.11, 0.14)	0.20 (0.08, 0.31)	0.05 (-0.12, 0.23)
Reversion indicator					
IGT	0.28 (0.07, 0.50)	0.28 (0.12, 0.45)	0.42 (0.19, 0.64)	0.10 (-0.04, 0.24)	—

Variable	AGI	Chinese medicine	Insulin sensitizer	Lifestyle modification	Vitamin D
IFG/IGT	0.51 (0.18, 0.85)	0.25 (0.01, 0.49)	0.41 (0.16, 0.65)	0.21 (0.08, 0.33)	0.05 (−0.25, 0.36)
IFG + IGT	—	0.44 (0.09, 0.78)	0.18 (0.05, 0.32)	0.27 (0.12, 0.42)	0.21 (−0.13, 0.56)
Baseline BMI (kg/m ²)					
<30	0.35 (0.19, 0.52)		0.34 (0.17, 0.51)	0.14 (0.03, 0.25)	0.21 (−0.13, 0.56)
30	0.04 (−0.25, 0.34)	—	0.17 (0.04, 0.30)	0.25 (0.13, 0.37)	0.05 (−0.17, 0.26)
Weight loss					
<4%	0.04 (−0.22, 0.31)		0.10 (−0.02, 0.23)	0.16 (0.04, 0.27)	
4%	0.55 (0.25, 0.86)	—	0.43 (0.21, 0.66)	0.26 (0.15, 0.38)	—
Follow up length					
12 months	0.49 (0.05, 0.93)	0.41 (0.22, 0.60)	0.44 (0.25, 0.63)	0.26 (0.13, 0.39)	0.04 (−0.35, 0.43)
>12 months	0.22 (0.07, 0.36)	0.21 (0.05, 0.37)	0.11 (0.01, 0.22)	0.11 (0.01, 0.20)	0.12 (−0.09, 0.34)

Notes: Bolded text indicates risk difference is significant between treatment and control. Estimates are intervention versus control risk difference (95% CI). Higher RD indicates greater normoglycemia difference between treatment and control arms.

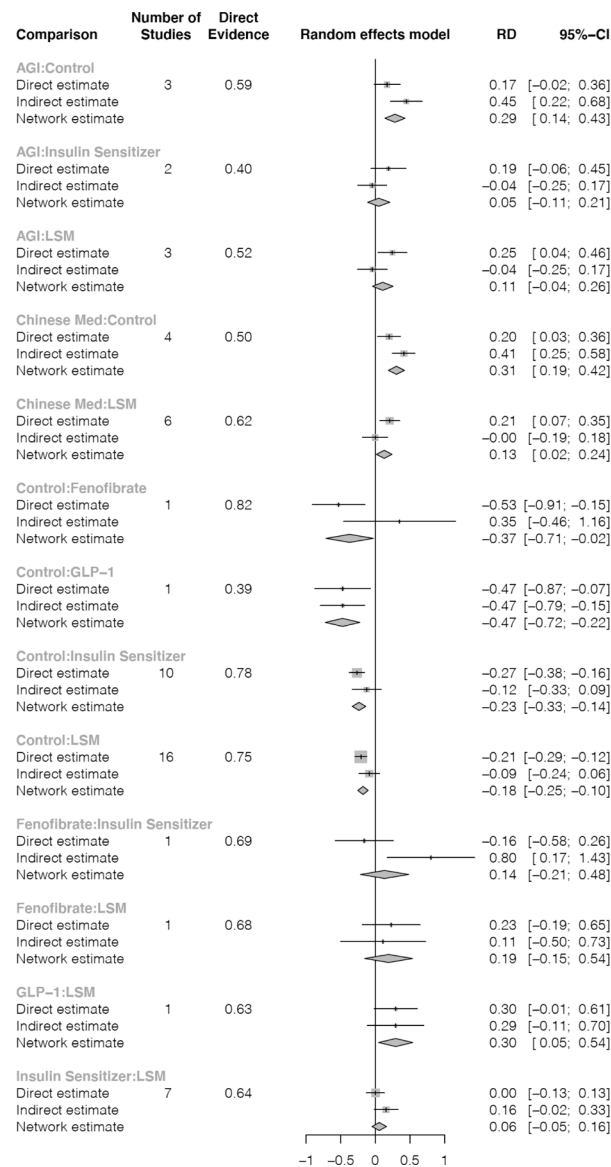
IFG, impaired fasting glucose; IGT, impaired glucose tolerance. These represent the indicator used to determine achievement of normoglycemia at the end of the intervention.

Appendix Table 4.

Sensitivity Analysis Including Low Risk of Bias Studies (N=34). Treatment Arms Are Compared Against Control/Placebo Arms

Treatment	RR (95% CI)	RD (95% CI)
AGI	1.61 (1.04, 2.48)	0.22 (0.03, 0.41)
Chinese medicine	2.72 (1.79, 4.11)	0.36 (0.20, 0.52)
Fenofibrate	1.90 (0.81, 4.45)	0.37 (0.01, 0.74)
GLP-1	3.48 (1.58, 7.63)	0.47 (0.20, 0.74)
Insulin secretagogue	1.37 (0.48, 3.87)	0.15 (−0.33, 0.63)
Insulin sensitizer	1.68 (1.22, 2.31)	0.27 (0.15, 0.39)
Lifestyle modification	1.71 (1.29, 2.27)	0.17 (0.07, 0.27)
L-arginine	1.92 (0.76, 4.85)	0.20 (−0.17, 0.57)
Lipase inhibitor	2.50 (1.05, 5.96)	0.40 (0.01, 0.79)
Magnesium	7.25 (2.10, 25.00)	0.44 (0.07, 0.80)
RAS blockade	1.11 (0.52, 2.39)	0.04 (−0.29, 0.38)
Vitamin D	1.38 (0.69, 2.78)	0.05 (−0.20, 0.29)

AGI, alpha glucosidase inhibitors; GLP-1, glucagon-like peptide 1 receptor agonists; RAS, renin-angiotensin system.

**Appendix Figure 3.**

Node-split showing risk difference obtained from direct treatment comparisons (i.e., in same study) and from indirect comparisons (i.e., obtained in this meta-analysis).

Appendix Table 5.

Results from the Grading of Recommendations Assessment, Development, and Evaluation (GRADE)

Treatment	GRADE	Rationale for grade
Lifestyle modification	⊕⊕⊕⊕ Strong	33% of studies have high risk of bias but this was mainly due to lack of blinding to intervention. Based on this, we concluded this should not downgrade the strength of the evidence.
Insulin Sensitizer	⊕⊕⊕⊖ Moderate	Downgraded by one level because 33% of studies had high risk of bias and given that observed heterogeneity was high ($P = 85\%$).

Treatment	GRADE	Rationale for grade
AGI	⊕ ⊕ ⊕ ⊖ Moderate	Downgraded by one level because 40% of studies have high risk of bias and given that the observed heterogeneity was moderate ($I^2 = 60\%$).
GLP-1	⊕ ⊕ ⊕ ⊖ Moderate	Downgraded by one level due to an imprecise effect estimate and given that the observed heterogeneity was moderate ($I^2 = 60\%$).
Chinese medicine	⊕ ⊕ ⊕ ⊖ Low	Downgraded by two levels because 30% of studies have high risk of bias, the effect estimate was imprecise, and given publication bias was present (Egger test $p < 0.001$).
RAS Blockade	⊕ ⊕ ⊕ ⊖ Low	Downgraded by two levels given that the confidence interval includes evidence of no effect and given there is a single study testing this treatment.
Insulin Secretagogue	⊕ ⊕ ⊕ ⊖ Low	Downgraded by two levels given that the confidence intervals include evidence of no effect and given there is a single study testing this treatment.
Vitamin D	⊕ ⊕ ⊕ ⊖ Low	Downgraded by two levels because 33% of studies have high risk of bias and given that the confidence intervals include evidence of no effect.
Magnesium	⊕ ⊖ ⊖ ⊖ Very Low	Downgraded by three levels because the effect estimate was imprecise and given that there is a single study at high risk of bias testing this treatment.
Lipase inhibitor	⊕ ⊖ ⊖ ⊖ Very Low	Downgraded by three levels due to the imprecise effect estimate and given that there is a single study at high risk of bias testing this treatment.
DPP-4	⊕ ⊖ ⊖ ⊖ Very Low	Downgraded by three levels given that the confidence intervals include evidence of no effect and given that there is a single study at high risk of bias testing this treatment.
Fenofibrate	⊕ ⊖ ⊖ ⊖ Very Low	Downgraded by three levels because the effect estimate was imprecise and given that there is a single study at high risk of bias testing this treatment.
L-Arginine	⊕ ⊖ ⊖ ⊖ Very Low	Downgraded by three levels given that the confidence intervals include evidence of no effect and given that there is a single study at high risk of bias testing this treatment.

AGI, alpha glucosidase inhibitors; DPP-4, dipeptidyl peptidase 4 inhibitors; GLP-1, glucagon-like peptide 1 receptor agonists; RAS, renin-angiotensin system.

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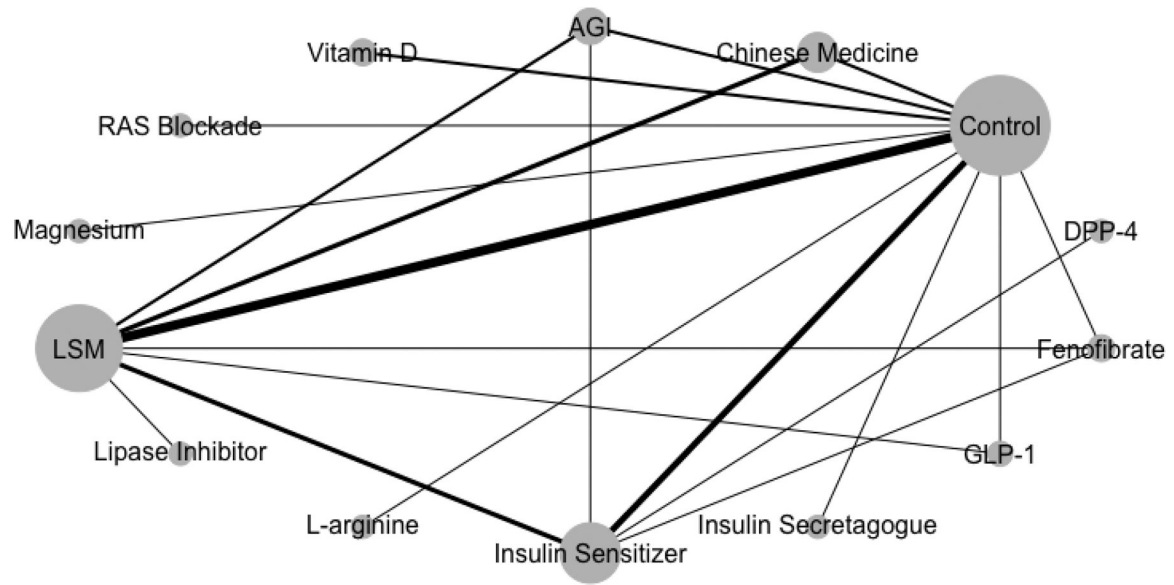
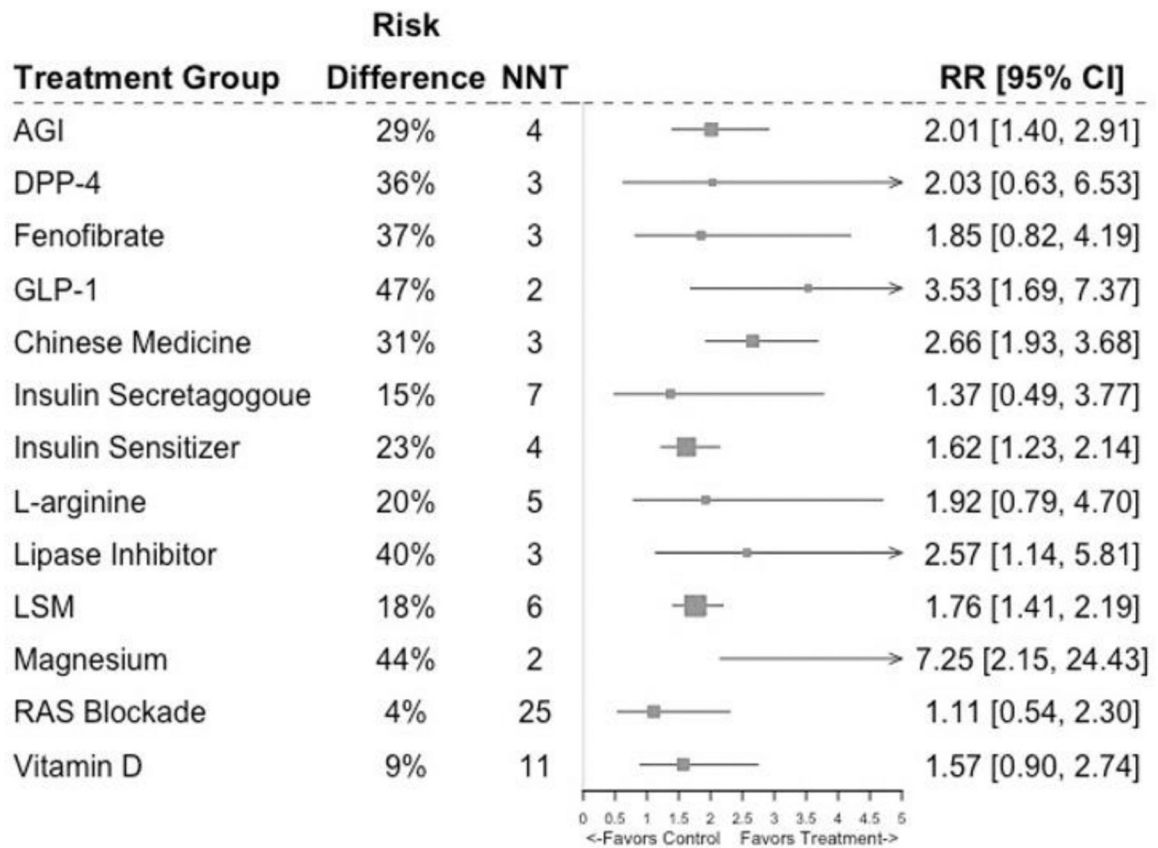


Figure 1.

Network structure showing an asymmetrical network.

Notes: The size of the bubble represents the number of studies testing a treatment and the thickness of the connecting lines the number of arms testing that comparison.

AGI, alpha-glucosidase inhibitors; DPP-4, dipeptidyl peptidase 4 inhibitors; GLP-1, glucagon-like peptide 1 receptor agonists; LSM, lifestyle modification; RAS, renin-angiotensin system.

**Figure 2.**

Forest plot showing pooled effects for each treatment against control/placebo.

AGI, alpha-glucosidase inhibitors; DPP-4, dipeptidyl peptidase 4 inhibitors; GLP-1, glucagon-like peptide 1 receptor agonists; LSM, lifestyle modification; RAS, renin-angiotensin system; NNT, number needed to treat; RD, risk difference; RR, relative risk.

Table 1.

Baseline Participant Characteristics Across Treatment Arms

Arms	Study participant characteristics							Normoglycemia ^a %
	Age (years)	Male sex	Race	Weight (kg) Mean (SD)	BMI (kg/m ²) Mean (SD)	FBG (mmol/l) Mean (SD)	PLG (mmol/l) Mean (SD)	A1c (%) Mean (SD)
Control (N=35; n=10,164)	52.9 (6.0)	44%	White 20%	84.9 (11.3)	29.7 (3.7)	5.9 (0.4)	8.5 (1.9)	6.0 (0.4)
Intervention (N=67; n=15,948)	53.1 (6.0)	40%	White 30%	84.5 (12.6)	29.4 (4.3)	5.8 (0.4)	8.6 (1.4)	6.0 (0.4)
AGIs (N=5; n=1,703)	57.3 (5.8)	55%	Asian 60%	79.9 (10.9)	26.3 (3.1)	6.1 (0.3)	8.9 (0.5)	5.5 (0.6)
DPP-4 (N=1; n=8)	49.3 (5.7)	38%	Latino 100%	84.3 (18.1)	31.3 (3.6)	5.5 (0.5)	8.9 (0.9)	6.1 (0.3)
Fenofibrate (N=1; n=20)	NR	0%	Asian 100%	NR	NR	NR	NR	NR
GLP-1 (N=2; n=1,488)	50.5 (4.2)	24%	White 83%	107.0 (0.8)	37.3 (2.1)	5.7 (0.3)	7.7 (0.4)	5.7 (0.1)
Chinese medicine (N=10; n=1,111)	51.6 (3.3)	46%	Asian 100%	66.7 (3.4)	25.6 (1.6)	6.0 (0.4)	9.0 (0.5)	6.4 (0.5)
Insulin secretagogues (N=1; n=16)	58.0 (2.0)	11%	White 100%	NR	27.9 (1.5)	5.3 (0.1)	7.7 (0.2)	NR
Insulin sensitizers (N=13; n=4,342)	52.3 (7.3)	38%	White 19%	85.3 (7.7)	30.5 (2.6)	5.6 (0.4)	8.9 (0.5)	5.9 (0.2)
L-arginine (N=1; n=66)	57.2 (11.7)	51%	White 100%	NR	30.4 (5.3)	5.8 (0.7)	9.1 (1.0)	NR
Lifestyle modification (N=27; n=4,065)	53.6 (6.1)	39%	Asian 44%	83.9 (12.5)	29.6 (5.1)	5.9 (0.4)	8.6 (2.2)	6.0 (0.4)
Lipase inhibitor (N=1; n=67)	43.9 (0.6)	19%	White 88%	99.0 (0.6)	35.6 (0.1)	5.8 (0.1)	NR	NR
Magnesium (N=1; n=59)	53.6 (6.1)	NR	Latino 100%	NR	30.6 (6.4)	6.3 (0.4)	7.7 (1.9)	NR
RAS blockade (N=1; n=2,623)	54.7 (10.9)	40%	Asian 44%	84.8 (18.8)	30.9 (5.6)	NR	NR	NR
Vitamin D (N=3; n=380)	56.3 (7.1)	66%	White 67%	102.6 (10.2)	29.6 (3.1)	6.0 (0.4)	7.7 (0.7)	6.1 (0.1)

^aCrude total percentage of participants that achieved normoglycemia at the end of the intervention.

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AGIs, alpha-glucosidase inhibitors; DPP-4, dipeptidyl peptidase 4 inhibitors; FBG, fasting blood glucose; GLP-1, glucagon-like peptide 1 receptor agonists; N, total number of arms; n, total number of participants; NR, not reported; PLG, 2-hour post-load glucose; RAS, renin-angiotensin system.

Table 2.

Risk Difference (95% CI) Relative to Control (First Column) and to Treatment

	CON	RAS	VIT-D	LSM	SEC	L-ARG	SEN	AGIs	DPP-4	CHIN	FEN	LIP	MAG
RAS	0.04 (-0.27; 0.35)												
VIT-D	0.09 (-0.09; 0.28)	-0.05 (-0.41; 0.31)											
LSM	0.18 (0.10; 0.25)	-0.13 (-0.45; 0.18)	-0.08 (-0.29; 0.12)										
SEC.	0.15 (-0.31; 0.61)	-0.11 (-0.66; 0.44)	-0.06 (-0.55; 0.44)	0.03 (-0.44; 0.49)									
L-ARG	0.20 (-0.14; 0.55)	-0.16 (-0.62; 0.30)	-0.11 (-0.50; 0.28)	-0.03 (-0.38; 0.32)	-0.05 (-0.62; 0.52)								
SEN	0.23 (0.14; 0.33)	-0.19 (-0.52; 0.13)	-0.14 (-0.35; 0.07)	-0.06 (-0.16; 0.05)	-0.08 (-0.55; 0.38)	-0.03 (-0.39; 0.33)							
AGIs	0.29 (0.14; 0.43)	-0.24 (-0.58; 0.10)	-0.19 (-0.43; 0.05)	-0.11 (-0.26; 0.04)	-0.13 (-0.61; 0.34)	-0.08 (-0.46; 0.29)	-0.05 (-0.21; 0.11)						
DPP-4	0.36 (-0.22; 0.94)	-0.32 (-0.97; 0.34)	-0.26 (-0.87; 0.35)	-0.18 (-0.76; 0.40)	-0.21 (-0.95; 0.53)	-0.16 (-0.83; 0.52)	-0.13 (-0.70; 0.45)	-0.07 (-0.67; 0.52)					
CHIN	0.31 (0.19; 0.42)	-0.26 (-0.59; 0.07)	-0.21 (-0.43; 0.01)	-0.13 (-0.24; -0.02)	-0.16 (-0.63; 0.32)	-0.10 (-0.47; 0.26)	-0.07 (-0.22; 0.07)	-0.02 (-0.20; 0.16)	0.05 (-0.54; 0.64)				
FEN	0.37 (0.02; 0.71)	-0.33 (-0.79; 0.14)	-0.27 (-0.67; 0.12)	-0.19 (-0.54; 0.15)	-0.22 (-0.79; 0.35)	-0.17 (-0.65; 0.32)	-0.14 (-0.68; 0.21)	-0.08 (-0.45; 0.29)	-0.01 (-0.68; 0.66)	-0.06 (-0.42; 0.30)			
LIP	0.40 (0.04; 0.76)	-0.36 (-0.83; 0.12)	-0.31 (-0.71; 0.10)	-0.23 (-0.58; 0.13)	-0.25 (-0.83; 0.33)	-0.20 (-0.70; 0.30)	-0.17 (-0.54; 0.20)	-0.12 (-0.50; 0.27)	-0.04 (-0.72; 0.64)	-0.10 (-0.47; 0.27)	-0.03 (-0.53; 0.46)		
MAG	0.44 (0.10; 0.78)	-0.40 (-0.85; 0.06)	-0.34 (-0.73; 0.05)	-0.26 (-0.61; 0.09)	-0.29 (-0.86; 0.28)	-0.23 (-0.72; 0.25)	-0.20 (-0.56; 0.15)	-0.15 (-0.52; 0.22)	-0.08 (-0.75; 0.59)	-0.13 (-0.49; 0.23)	-0.07 (-0.55; 0.41)	-0.04 (-0.53; 0.46)	
GLP-1	0.47 (0.22; 0.72)	-0.43 (-0.83; -0.03)	-0.38 (-0.69; -0.06)	-0.30 (-0.54; -0.05)	-0.32 (-0.84; 0.20)	-0.27 (-0.69; 0.16)	-0.24 (-0.50; 0.03)	-0.19 (-0.47; 0.10)	-0.11 (-0.74; 0.52)	-0.17 (-0.43; 0.10)	-0.10 (-0.52; 0.32)	-0.07 (-0.50; 0.36)	-0.03 (-0.45; 0.39)

Note: The table reads top to bottom, starting with the first column/row and moving down within the column to each row below. Estimates are ranked according to effect size from top to bottom, and by significance level from left to right. Bolded text indicates significant estimates.

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AGI, alpha-glucosidase inhibitors; L-ARG, L-arginine; CHIN, Chinese medicine; DPP-4, dipeptidyl peptidase 4 inhibitors; FEN, fenofibrate; GLP-1, glucagon-like peptide 1 receptor agonists; LIP, lipase inhibitor; LSM, lifestyle modification; MAG, magnesium; SEN, insulin sensitizers; SEC, insulin secretagogue; RAS, renin-angiotensin system; VIT-D, vitamin D.