Supplementary Online Content

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eTable 1. Search Terms and Combination MeSH Terms Used

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eFigure 1. Meta-Regression Examining the Influence of Weight Lost on Diabetes Risk Among Studies Reporting This Outcome

eFigure 2. Funnel Plot Exploring Publication Bias

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Search Terms and Combination MeSH Terms Used

Search Terms	Combinations	Filters
diabetes prevention,	"Prediabetes" OR	18+ years
impaired glucose tolerance,	"Pre diabetes" OR	Clinical trials
glucose intolerance,	"Impaired glucose tolerance" OR	Humans
impaired fasting glucose,	"impaired" AND "fasting" AND "glucose" OR	Publication year 1990+
prediabetic state,	"diabetes" OR	
prediabetes,	"diabetes" AND "mellitus" AND "type 2" AND	
diabetes mellitus type 2,	"prevention" OR	
type 2 diabetes mellitus,	"disease" AND "prevention" OR	
prevention,	"risk" OR	
primary prevention,	"risk" AND "reduction"	
disease prevention,	NOT gestational	
risk reduction,		
risk reduction behavior.		

eTable 2. Characteristics of Included and Analyzed Studies

Author (Year) Trial, Country	Sample Analyzed	BMI kg/m^2 (baseline*)	% Male (baseline*)	Median** Follow up	Intervention/Drug Tested and Maintenance/Washout Duration	DM Diagnostic Criteria	Quality category (score)***
LIFESTYLE STUDIES							
Lindstrom, (2013)[1] DPS, Finland	n = 366 with IGT	31	33%	9 years	Intervention group met regularly to receive counseling from nutritionist to achieve ≥ 5% weight loss, moderate intensity physical activity ≥ 30 min/day, and fat < 30% of total calories. Control group received lifestyle and diabetes information in one session.	WHO 1985	Medium (6)
Wong (2013)[2] China	n = 104 with IGT or IFG	25.9	93%	2 years [max]	Treatment group received text message information about diabetes, lifestyle modification, and encouragement. Control group received usual care. Participants in both groups were given information booklets on pre-diabetes, diabetes, and health behavior information.	WHO 2006	Medium (6)
Xu (2013)[3] China	n = 81 with IGT or IFG	26.3	48%	1 year [max]	Treatment group received coaching on low-glycemic foods and exercise and daily low-glycemic meal replacement for first 3 months of the study and monthly follow-up visits thereafter. Control group received one counseling session at baseline.	ADA 2003	Medium (6)
Gagnon (2011)[4] Canada	n = 48 with IGT or IFG	35.1	46%	1 year [max]	Group one met individually with nurse, dietitian, and endocrinologist; in group seminars received diet, exercise, and weight loss counseling. Group two was offered group seminars only.	WHO 1999	Medium (4)
Moore (2011)[5] Australia	n = 274 with IGT or IFG	29.7	41%	0.5 years [max]	Intervention group received pre-course individual session then 6 educational group sessions based on behavior change. Control group received intervention after 6 months of usual care.	WHO 1985	Medium (5)
Saito (2011)[6] Japan	n = 621total with IFG+IGT or isolated IFG	27.0	71%	3 years [max]	Frequent intervention group received individual diet and exercise coaching at least 9 times in 36 months from medical professionals. Control group received similar coaching once a year for 3 years	WHO 2006	Medium (5)
Sakane (2011)[7] Japan	n = 213 with IGT	24.5	50%	3 years [max]	Treatment group received diabetes, diet and exercise counseling in 4 group meetings over 6 months and biannual individual follow-up meetings over 3 years. Control group attended one group session on	WHO 2006	Low (3)

					healthy lifestyle.		
Zhou (2011)[8] China	n = 117 with IGT or IFG	24.5	30%	0.5 years [max]	Interventions included: 1) individualized diet plan controlling nutrients and total energy intake, adjusted once a month; 2) exercise program including walking, jogging, dancing and taichi, with five 40-minute sessions per week; 3) combined diet and exercise programs; 4) control group.	Not Reported	Low (3)
Kang (2010)[9] South Korea	n =85 with IFG	25.6	100%	2 years [max]	Face-to-face counseling based on the participant's health profiles for 12 weeks with email follow-up after primary intervention, focused on achievable diet and exercise goals for 2 years. Control group received usual care.	ADA 1997	Medium (5)
Diabetes Prevention Program Research Group (2009)[10] DPPOS, USA	n = 1842 with IGT and IFG	33.2	32%	10 years	10-year follow-up study of DPP. Participants in all groups were offered a group-administered version of the DPP 16-session lifestyle curriculum. Maintenance strategy/duration: lifestyle sessions (HELP) were offered every 3 months to reinforce 7% weight loss and 150+ min of physical activity/week for all. The lifestyle group was also offered two group classes (BOOST) each comprising four sessions every year. Participants in control group were also offered the group lifestyle modification program.	ADA 1997	High (8)
Penn (2009)[11] EDIPS, UK	n = 102 with IGT	34	41%	3 years [max]	Intervention group received individual advice from dietician and physiotherapist trained in motivational interviewing; individualized plan to decrease energy intake from carbs and fat, increase fiber and physical activity, and achieve normal BMI. Control group received standard health promotion advice.	WHO 1999	Medium (5)
Kawahara (2008)[12] Japan	n = 285 with IGT	24.6	47%	3.1 years [mean]	Hospitalization group received exercise advice and individual diet plan during 1-3-day hospitalization. Education and support group received periodic counseling with clinicians about healthy lifestyle. Control group received usual care. Maintenance: individual counseling sessions every 3 months over three years	ADA 2003	Medium (6)
Li (2008)[13] Da Qing, China	n = 576 with IGT	25.8	54%	20 years [max]	20-yr follow-up of Da Qing Study. Diet group counseled on healthy diet and losing weight if overweight/obese. Exercise group individually counseled on increasing physical activity. Combined group received diet & exercise counseling. Control group received brochures about IGT and diabetes.	WHO 1985	Medium (5)
Roumen (2008)[14] SLIM, Netherlands	n = 106 with IGT	29.4	51%	3 years [max]	Intervention group received diet & exercise counseling from dietician for 60 minutes every 3 months. Encouraged to exercise 30 minutes/day, 5 days/week. Control group received brief information	WHO 1999	Low (2)

					about benefits of a healthy diet.		
Oldroyd (2006)[15] UK	n = 54 with IGT	Not Reported	57%	2 years [max]	Intervention group received regular counseling from a dietician and physiotherapist using the stages-of-change model of behavior change. Control group instructed to maintain pre-study habits.	WHO 1985	Medium (5)
Ramachandran (2006)[16] IDPP, India	n = 253 with IGT	26.0	77%	2.5 years	Lifestyle modification group encouraged to exercise 30 min/day and improve diet during monthly phone calls and in person every six months. Control group received usual care.	WHO 1999	Medium (5)
Kosaka (2005)[17] Japan	n = 458 with IGT	23.8	100%	4 years [max]	Intensive intervention group counseled to achieve BMI < 22.0 with diet and exercise at hospital visit every 3-4 months. Control group advised to maintain BMI < 24.0 at hospital visit every 6 months.	WHO 1985	Medium (4)
Diabetes Prevention Program Research Group (2002)[18] DPP, USA	n = 2161 with IGT and IFG	34.0	32%	2.8 years [mean]	Lifestyle modification program contained 16 individual counselling sessions on diet, exercise, and behavior modification over 24 weeks. Goals were 7% weight loss and ≥150 min physical activity per week. Maintenance: subsequent individual sessions (usually monthly) and group sessions. Control group received a placebo tablet twice daily.	ADA 1997	High (8)
Liao (2002)[19] USA	n = 58 with IGT	26.1	45%	2 years [max]	Treatment group received endurance exercise training and advised to maintain isocaloric American Heart Association step 2 diet. Control group performed stretching exercises three weekly for 1 h and were prescribed an isocaloric American Heart Association step 1 diet.	WHO 1999	Medium (4)
Swinburn (2001)[20] New Zealand	n = 103 with IGT	29.1	74%	5 years [max]	Treatment group received education about reducing fat intake at monthly group meetings for 1 year. Control group maintained normal diet.	WHO 1999	Low (2)
Tuomilehto (2001)[21] DPS, Finland	n = 522 with IGT	31	33%	6 years [max]	7 one-one one counselling in year 1, then every three months up to year 6 plus optional group classes. Intervention group received counseling from nutritionist to achieve ≥ 5% weight loss, moderate intensity physical activity ≥ 30 min/day, and fat < 30% of total calories. Control group received lifestyle and diabetes information in one session.	WHO 1985	Medium (6)
Pan (1997)[22] Da Qing, China	n = 530 with IGT	25.8	50%	6 years [max]	Diet group counseled by physicians on healthy diet and losing weight if overweight/obese. Exercise group individually counseled on increasing leisure physical activity. Combined treatment group received diet & exercise counseling, similar to those described above. All groups met weekly for one month, monthly for 3 months, then every 3 months for duration of the study. Control group received	WHO 1985	Medium (5)

					brochures about IGT and diabetes.		

MEDICATION STUDIES							
Garvey (2014)[23] SEQUEL, USA	n = 315 with IGT or IFG	36.2	35%	1 year	Treatment groups received phentermine/topiramate 7.5/46 or phentermine/topiramate 15/92 once daily. Control group received once daily placebo. Lifestyle modification counseling based on the LEARN (lifestyle, exercise, attitudes, relationships, and nutrition) program for all participants.	WHO 1999	High (7)
Kataoka (2012)[24] DIANA, Japan	n = 175 with IGT	24.3	86%	1 year [max]	Treatment group took nateglinide 60 mg 3 times daily or voglibose 0.3mg 3 times daily. Control group did not take placebo. All participants were encouraged to start a low-calorie diet and mild to moderate exercise.	WHO 1999	High (7)
ORIGIN Trial Investigators (2012)[25] ORIGIN	n = 1452 with IFG or IGT	29.9	65%	6.2 years	In a 2x2 factorial design, participants received insulin glargine or standard care *and* n-3 fatty acids or placebo. Washout duration: 14 weeks	Not Reported	Medium (6)
Barzilay (2011)[26] TRANSCEND	n = 1561 with IFG and/or IGT	27.6	61%	4.7 years	Treatment group received telmisartan 80 mg daily. Control group received placebo.	WHO 1999	High (7)
DeFronzo (2011)[27] USA	n = 441 with IGT	33.7	48%	2.4 years	Treatment group received pioglitazone 30 mg once daily for first month, then 45 mg per day. Control group received placebo. All participants received 30 minutes of DPP instruction from dietician or nurse, with emphasis on decreased total caloric intake, decreased fat intake, and walking 30 minutes per day 4-5 days per week.	ADA 2003	Medium (5)
Lu (2011)[28] China	n = 181with IGT or IFG	27.0	53%	2 years [max]	Intervention participants with IGT received acarbose 50 mg 3 times daily; those with IFG received metformin 250 mg 3 times daily. All intervention participants received lifestyle coaching in person every 3 months and by phone monthly. Control group received basic education and usual care.	ADA 2003	Low (3)
The NAVIGATOR Study Group (2010)[29] NAVIGATOR valsartan trial	n = 9306 with IGT	30.5	49%	5 years	In 2x2 factorial design, patients took valsartan 160 mg once daily or placebo *with/without* nateglinide up to 60 mg three times daily and/or placebo. All subjects participated in a clinic-based and telephone-based lifestyle modification program.	WHO 1999	High (7)
The NAVIGATOR Study Group (2010)[30] NAVIGATOR	n = 9306 with IGT	30.5	49%	5 years	In 2x2 factorial design, patients took nateglinide 160 mg once daily or placebo *with/without* valsartan up to 60 mg three times daily and/or placebo. All subjects participated in a clinic-based and telephone-based lifestyle modification program.	WHO 1999	High (7)

nateglinide trial							

Zinman (2010)[31] CANOE, Canada	n = 207 with IGT	31.7	33%	3.9 years	All patients participated in one-on-one lifestyle coaching in first year and received educational materials thereafter. Treatment received Metformin 500 mg and rosiglitazone 2 mg twice daily. Control group received placebo.	WHO 2006	High (7)
Diabetes Prevention Program Research Group (2009)[10] DPPOS, USA	n = 1856 with IGT and IFG	32.1	32%	10 years	10-year follow-up study of DPP. Participants in all groups were offered a group-administered version of the 16-session lifestyle curriculum. Metformin group continued 850mg twice daily.	ADA 1997	High (8)
Kawamori (2009)[32] Japan	n = 1778 with IGT	25.8	60%	3 years	Intervention group received voglibose 0.2 mg three times daily. Control group received placebo. Voglibose and control groups both received individual counseling on healthy diet and exercise.	WHO 1999	High (7)
Nijpels (2008)[33] DAISI, Netherlands	n = 118 with IGT	28.9	50%	3 years [max]	Treatment group received acarbose, titrated up to max of 50 mg three times daily. Control group received placebo.	WHO 1985, WHO 1999	Medium (5)
DREAM Trial Investigators, (2006 and 2011)[34,35] DREAM	n = 5269 with IFG and/or IGT	30.9	41%	3 years	Treatment group received rosiglitazone 8 mg daily (titrated up from 4 mg daily). Control group received placebo. Washout duration: 10 weeks	WHO 1999	High (7)
DREAM Trial Investigators (2006 and 2011)[35,36] DREAM	n = 5269 with IFG and/or IGT	30.9	41%	3 years	In a 2x2 factorial design, participants received ramipril 15 mg daily (titrated up from 5 mg daily) or placebo *and* rosiglitazone or placebo. Washout duration: 10 weeks	WHO 1999	High (7)
Eriksson (2006)[37] Botnia study, Finland	n = 34 with IGT	28.3	56%	1.5 years [max]	Treatment group received glipizide 2.5 mg daily for 6 months. Control group received placebo. Washout duration: 52 weeks	WHO 1999	Medium (4)
Ramachandran (2006)[16] IDPP, India	n = 261 with IGT	25.9	78%	2.5 years	Metformin group received 250 mg Metformin twice daily. Control group received usual care.	WHO 1999	Medium (5)

Tenenbaum (2005)[38] BIP, Israel	n = 339	32.4	85%	6.3 years [mean]	All participants received standard lipid-lowering dietary advice in three 15-minute interventions. Treatment group received bezafibrate 400 mg once daily. Control received placebo.	ADA 1997	Medium (4)
Torgerson (2004)[39] XENDOS, Sweden	n = 3277 with BMI ≥ 30 and IGT	37.3	45%	4 years [max]	All participants were prescribed a reduced-calorie diet (800 kcal/day deficit) and received dietary counseling. Encouraged to walk at least 1 extra kilometer per day. Treatment group received orlistat 120 mg with breakfast, lunch, and dinner.	2hr OGTT ≥ 10 mmol/L	Medium (6)
Kanaya (2003)[40] HERS, USA	n = 218 with IFG	28.7	0%	4.1 years [mean]	Treatment group received 0.625 mg of conjugated estrogen plus 2.5 mg of medroxyprogesterone acetate daily. Control group received placebo.	ADA 1997	High (8)
Chiasson (2002)[41] STOP-NIDDM	n = 1368 with IGT	30.9	49%	3.3 years [mean]	All participants received weight loss counseling from dietician yearly. Treatment group received acarbose 50-100 mg 3 times per day with meals (mean dose 194 mg, SD 87 mg). Control group received placebo. Washout duration: 12 weeks	WHO 1985	Medium (6)
Diabetes Prevention Program Research Group (2002 and 2003)[18,42] DPP, USA	n = 2155 with IGT and IFG	34.0	32%	2.8 years [mean]	Metformin group received 850 mg twice daily. Control group received placebo. Washout duration: 2 weeks	ADA 1997	High (8)
Li (1999)[43] China	n = 70 with IGT	26.2	71%	1 year [max]	Patient education on healthy diet and exercise and diabetes prevention was provided every three months to all participants. Treatment group received metformin 250mg 3 times daily for 6 months. Control group received placebo.	WHO 1995	Medium (5)
STUDIES NOT INCLUDED IN META-ANALYSES (n=10)							
Perreault (2012)[44] DPPOS, USA	n = 1990 with IGT and IFG	Lifestyle group goal to achieve 7% weight loss and 150+ min physical activity/week through group lifestyle coaching. Metformin group received 850mg twice daily. Placebo group received placebo twice daily.				ADA 2003	Low (3)
Mason (2011)[45] USA	n = 439 postmenopausal women with BMI ≥ 25.0 and/or IFG	Exercise group exercised 3 days/week with supervision and 2 days/week at home. Diet group received individual coaching from dietician, met in groups weekly to achieve diet of 1,200-2,000 kcal/day, < 30% calories from fat. Exercise + diet group received both interventions. Control group received usual care.				N/A	Medium (5)

Lindstrom (2006)[46] DPS, Finland	n = 475 with IGT	7-yr follow-up of DPS. Intervention group met regularly to receive counseling from nutritionist to achieve ≥ 5% weight loss, moderate intensity physical activity ≥ 30 min/day, and fat < 30% of total calories. Control group received lifestyle and diabetes information once. Post-intervention follow-up: all participants had yearly visits with study nurse without specific diet or exercise counseling.	WHO 1985	Medium (6)
Ebbesson (2005)[47] USA	n = 454 Eskimos	Intervention participants received four 30-60 minute counseling sessions over 3 years that encouraged more traditional foods, fewer processed foods, and more physical activity. Control group one personal counseling session.	WHO 1985	Low (2)
Diabetes Prevention Program Research Group (2005)[48] DPP, USA	n = 2343 with IGT and IFG	Treatment group received troglitazone 400 mg once daily. Other treatment groups received metformin 850 mg twice daily, intensive lifestyle intervention, or placebo.	WHO 1985 & ADA 1997	Medium (4)
Lindstrom (2003)[49] DPS, Finland	n = 522 with IGT	Intervention group met regularly to receive counseling from nutritionist to achieve ≥ 5% weight loss, moderate intensity physical activity ≥ 30 min/day, and fat < 30% of total calories. Control group received lifestyle and diabetes information in one session.	WHO 1985	Medium (6)
Lindstrom (2003)[50] DPS, Finland	n = 522 with IGT	Intervention group met regularly to receive counseling from nutritionist to achieve ≥ 5% weight loss, moderate intensity physical activity ≥ 30 min/day, and fat < 30% of total calories. Control group received lifestyle and diabetes information in one session.	WHO 1985	Medium (6)
Li (2002)[51] DA Qing, China	n = 284 with IGT	Diet group counseled on healthy diet and losing weight if overweight/obese. Exercise group individually counseled on increasing physical activity. Combined group received diet & exercise counseling. Control group received brochures about IGT and diabetes.	WHO 1985	Medium (5)
Oldroyd (2001) UK[52]	n = 67 with IGT	Intervention group received regular counseling from a dietician and physiotherapist using the stages-of-change model of behavior change. Control group instructed to maintain pre-study habits.	WHO 1985	Medium (5)
Rosenstock (2010)[53] USA	n = 151 with IFG or IGT	Exenatide group received 10 mcgs daily after 4-week 5 mcg daily initiation period and structured program of diet and physical activity through week 24. Control group received lifestyle education and placebo.	WHO 2006	Medium (5)

*Baseline BMI and % male include all participants enrolled at baseline

**Median follow-up time reported, unless otherwise indicated. Follow-up time reported is corresponds to time point used in person-years estimate. IGT= Impaired glucose tolerance; IFG= Impaired fasting glucose; Max = maximum years of follow-up; Mean = mean years of follow-up

***A composite quality score was obtained by summing the scores across 4 quality indicators (blinding, attrition, analysis, and reporting). Studies scoring 0-3 points were classified as "low quality"; studies scoring 4-6 as medium quality; and studies scoring 7-8 as high quality.

Trial abbreviations: BIP, Bezafibrate Infarction Prevention Study; DPS, Diabetes Prevention Study; TLGS, Tehran Lipid and Glucose Study; DPPOS, Diabetes Prevention Program Outcomes Study; EDIPS, European Diabetes Prevention Study; SLIM, Study on lifestyle-intervention and impaired glucose tolerance Maastricht;IDPP, Indian Diabetes Prevention Programme; DPP, Diabetes Prevention Program; DIANA, DIAbetes and diffuse coronary NArrowing; ORIGIN, Outcome Reduction With Initial Glargine Intervention; TRANSCEND, Telmisartan Randomised AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease; NAVIGATOR, Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research; CANOE, CAnadian Normoglycemia Outcomes Evaluation; DAISI, Dutch Acarbose Intervention Study in Impaired glucose tolerance; DREAM,Diabetes REduction Assessment with ramipril and rosiglitazone Medication; ; HERS, Heart and Estrogen/Progestin Replacement Study; STOP-NIDDM, Study to Prevent NIDDM; XENDOS, Xenical in the Prevention of Diabetes in Obese Subjects; L-ARG, L-arginine trial.

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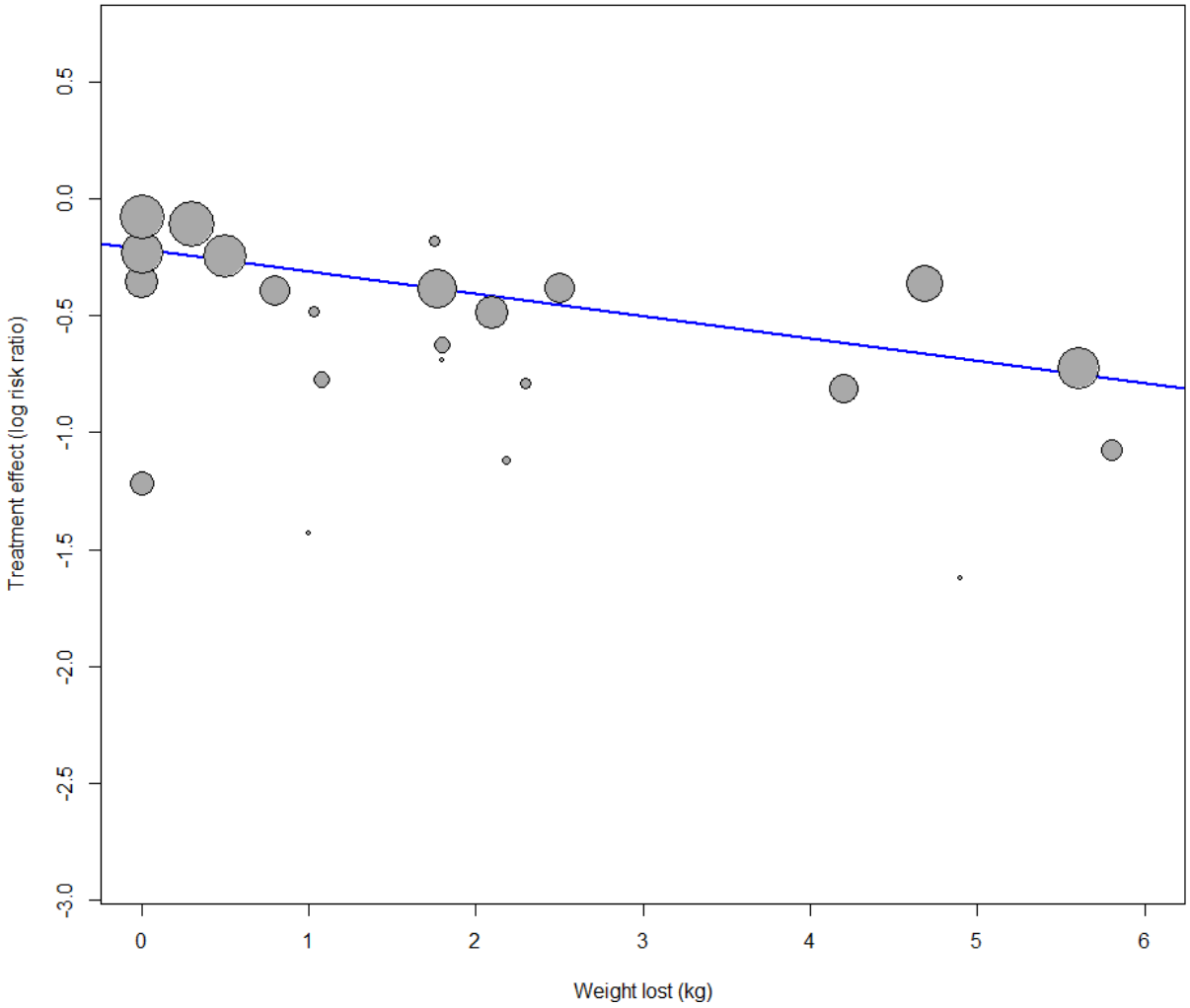
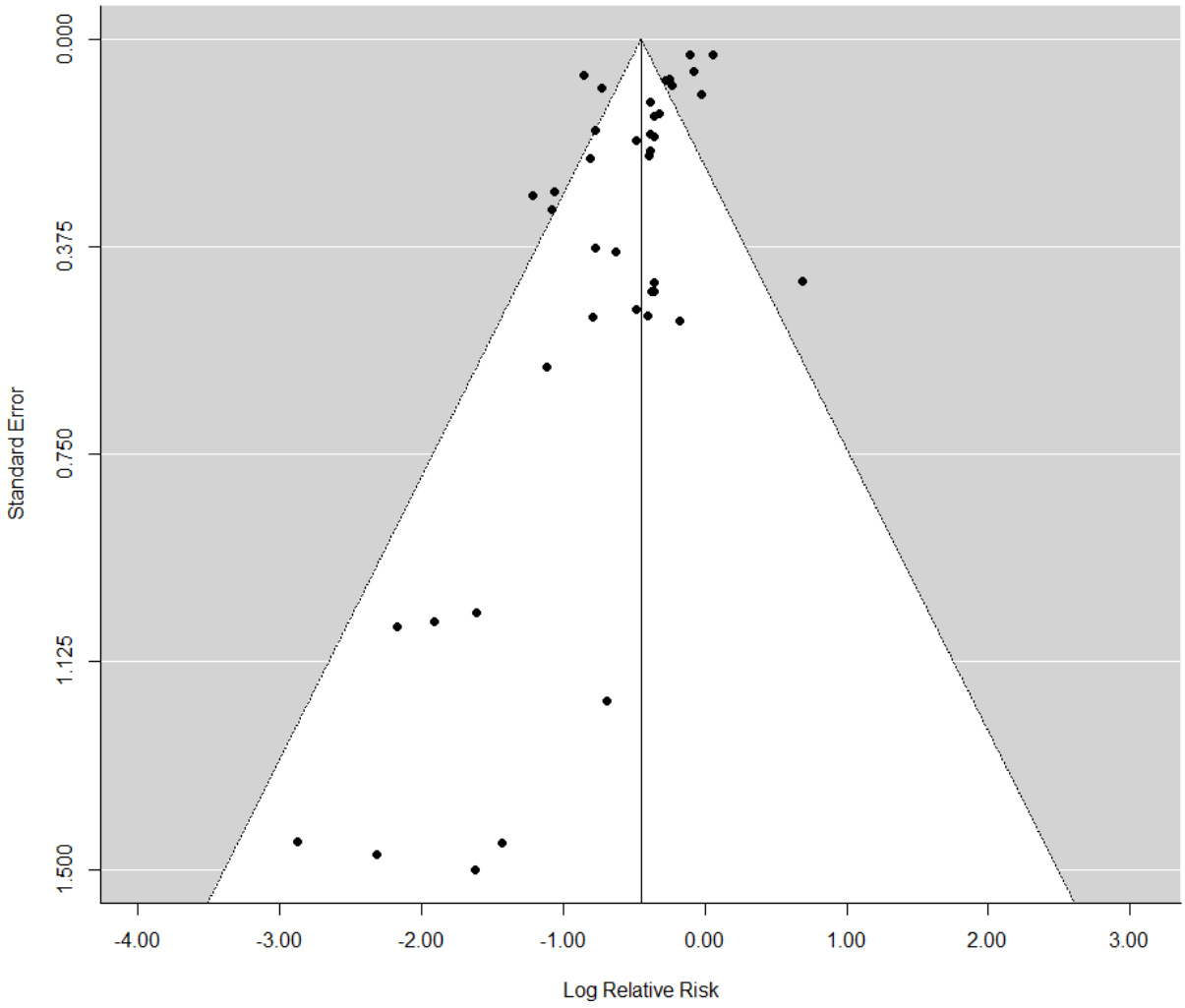
eFigure 1. Meta-Regression Examining the Influence of Weight Lost on Diabetes Risk Among Studies Reporting This Outcome (*N*=24).



A meta-regression including participant mean age, proportion of male participants and weight lost in kilograms as predictors of diabetes risk explained 59% of effect heterogeneity (p<0.01). The model shows that every kilogram of weight lost is associated with a 7% decrease in diabetes risk (β= -0.07, p<0.01), while age (β=0.008 p=0.64) and gender (β=0.003, p=0.61) did not have an influence.

eFigure 2. Funnel Plot Exploring Publication Bias



*Funnel plot examining publication bias. Each dot represents a study arm (*N*=40) plotted according to their effect (x axis) and their standard error (y axis). The asymmetrical plot indicates that smaller studies with null effects are less likely to be published (right side of the funnel) than studies with positive effects (left side of the funnel; t = -4.1, df = 39, p < 0.001).

