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Global Approaches to Diabetes Prevention:

A Systematic Review and Meta-Analysis

of Randomized Controlled Studies

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2006 & 2002

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An abstract of
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Abstract

Global Approaches to Diabetes Prevention: A Systematic Review and Meta-Analysis of Randomized Controlled Studies

By Veena Ramanna

Background: Clinical trials conducted in controlled research settings have shown strong evidence that lifestyle modifications, pharmacotherapeutic approaches and dietary supplement interventions can reduce the risk of diabetes incidence in the prediabetes population. This systematic review summarizes evidence gathered from randomized controlled trials where the impact of diverse approaches to prevent diabetes is evaluated in global settings.

Methods: A systematic search on Medline was performed to identify peer reviewed articles published between January 1, 1990 and October 22, 2019. These randomized controlled trials included individuals with prediabetes >19 years old, testing diabetes prevention interventions of at least 6 months duration, that reported diabetes incidence. Risk of bias for each study was assessed using the Cochrane collaboration. A random effects meta-analysis was employed to obtain a pooled relative risk for diabetes development by intervention type. Meta-regressions were employed to explore sources of heterogeneity for treatment effects.

Results: We included 65 studies (n=56,562 & 90,439, mean age=54.7 years, males =53% & 55.6% in the intervention and control groups respectively. White/European participants were reported in 33 studies). Of these, 31 tested lifestyle modification approaches, 25 pharmacotherapeutic approaches, and 9 dietary supplements. Studies were deemed to have low risk of bias. Lifestyle modification associated with a 31% relative risk reduction (RR = 0.69 [95% CI 0.61, 0.79]) and medications associated with a 37% relative risk reduction (RR = 0.63 [95% CI 0.54, 0.75]). Supplements did not significantly reduced diabetes risk (RR = 0.74 [95% CI 0.61, 0.74]). A meta-regression including participant weight loss explained 68.3% and 17% of heterogeneity in effects in the lifestyle and pharmacotherapeutic interventions, respectively (R^2=68.27%, p=0.0014 and R^2=16.78%, p=0.0877).

Conclusion: Globally, lifestyle modification and pharmacotherapeutic approaches effectively decrease the incidence of type 2 diabetes in adults at risk. National level diabetes programs should continue to be rolled out to halt diabetes incidence.

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Introduction

The Burden of Type 2 Diabetes

Type 2 Diabetes is a chronic progressive metabolic disease that encompasses multiple disorders related to altered metabolic homeostasis of glucose[1]. Type 2 Diabetes is the most common form of diabetes, accounting for about 95% of all diabetes cases globally[2]. The global prevalence of diabetes in adults is 8.8% and is expected to increase to 9.9% by 2045[3]. About 79% of adults with diabetes live in low and middle income countries[4]. Increase in these estimates will take place in regions where economies are moving from low income to middle income levels.

Chronic and acute diseases in the general population has risen due to increase in diabetes prevalence, with profound effects on quality of life, demand on health services and economic costs. Macrovascular complications of diabetes that are responsible for much of the burden associated with diabetes include coronary heart disease, stroke and peripheral vascular disease. Microvascular complications, such as end-stage renal disease, retinopathy and neuropathy, along with lower-extremity amputations. Conditions such as cancers, ageing-related outcomes (e.g. dementia), infections, and liver disease are also linked to diabetes[5]. Approximately 46.1% of deaths are due to diabetes for people under the age of 60[4].

Diabetes has been associated with an approximate 75% increase in mortality rate in adults, and the average 60 year old person diagnosed with diabetes loses 5 years of his or her life to the disease[6]. National Vital Statistics data[7] suggest that the mortality rate attributed to diabetes decreased by 16% from 2000, to 2010. However, deaths caused by diabetes itself are difficult to interpret because of awareness, changing prevalence, and under-reporting of diabetes as a contributing cause[8]. Thus, determination of the causes and trends in death associated with

diabetes requires follow-up mortality data based on cohorts of people with and without diabetes[9]. The reduction in relative risk of all-cause and vascular-disease death associated with diabetes should not be interpreted as an indication that the public health burden of diabetes is declining. The diversification of morbidity and mortality associated with diabetes could take different forms in different countries where risk factors, health status, medical care, and health monitoring/surveillance differ. The increasing diversification of the causes of death among people with diabetes will have important implications for the development of therapies and public health approaches to reduce diabetes-related morbidity[9].

In 2017, total global healthcare expenditures for diabetes amongst the older individuals (70 to 99 years) was $727 billion, which corresponds to one for every eight dollars spent on healthcare. The economic burden of diabetes is expected to increase to $776 billion by 2045[4]. As per the global estimate, 212.4 million people or half (50.0%) of all people aged 20-79 years with diabetes are unaware of their disease. Higher usage of healthcare services is seen in people with undiagnosed diabetes compared to people without diabetes. The total economic cost of undiagnosed diabetes was $33 billion in 2012[10]. Life expectancy and costs associated with frequency of diabetes-related complications in later stages of life are the reasons behind the large healthcare expenditure observed in the 60-69 years age group. Higher healthcare expenditure in diabetes has been observed in women in earlier stages of life than men[4].

Risk Factors

Several risk factors are associated with the development of diabetes. The most prominent risk factor is the presence of prediabetes. Prediabetes is a state of elevated blood glucose levels that do not reach Type 2 diabetes diagnostic thresholds. Prediabetes presents as impaired fasting

glucose (IFG), and/or impaired glucose tolerance (IGT) and/or Hemoglobin A1c (A1c) between 5.6-6.4% [11]. As per International Diabetes Federation criteria, 7.5% (374 million) of people aged 20–79 years are living with prediabetes globally[12]. The chances of developing Type 2 diabetes mellitus, within a year, in individuals with untreated prediabetes is 5-10%[13]. According to an expert panel from the American Diabetes Association up to 70% of individuals with prediabetes will eventually develop diabetes[13].

Diabetes develops as a result of acquired abnormalities that affect insulin sensitivity and insulin secretion, cause Type 2 diabetes. Currently available data suggest that impaired insulin secretion is the major genetic factor and insulin resistance is the acquired defect largely secondary to unhealthy lifestyles. Impaired insulin secretion is the result of both reduced β-cell mass and functional abnormalities preventing β-cells from effectively compensating for increased insulin requirements caused by insulin resistance. Targeting both insulin resistance and impaired insulin secretion is therefore the goal of preventive treatments [14].

Genetic, environmental and behavioral factors contribute to insulin resistance and secretion, and eventually to diabetes development[15]. Advances in the field of genetics has allowed for the identification of numerous genetic variants that are associated as risk factor with Type 2 diabetes. More than 120 variants have been convincingly replicated for association with Type 2 diabetes and many more with diabetes-related traits[16]. For example, the first candidate gene reproducibly associated with Type 2 diabetes was *PPARG*, encoding the nuclear receptor PPAR-γ. This variant has been shown to be associated with increased transcriptional activity, increased insulin sensitivity and protection against Type 2 diabetes[17]. However, many of these variants only explain a small proportion of the total heritability of Type 2 diabetes[16].

Increase in fasting insulin (FI), fasting glucose (FG), systolic blood pressure (SBP), high density lipoproteins (HDL), triacylglycerides (TAG), and body mass index (BMI) are associated with increased risk of developing diabetes[18]. Lifestyle factors related to obesity, namely diet and physical activity, play a major role in the prevention of Type 2 diabetes. Physical activity may increase insulin sensitivity, glucose disposal and free fatty acids oxidative capability[19]. High levels of physical activity is associated with a lower risk of diabetes within all categories of body mass index, but there is no clear evidence that being physically active could entirely compensate for the adverse effect of adiposity on diabetes risk[20]. Overweight status is associated with a complex pattern of energy intake and energy expenditure behaviors including types of nutrient intake and time in physical and sedentary activities[21].

Efficacy of Diabetes Prevention Approaches

Numerous prevention approaches have been tested and shown to be efficacious for preventing or delaying diabetes onset[22,23,24]. These interventions include lifestyle modifications, diverse pharmacotherapeutics and dietary supplements. The effects of these diabetes prevention approaches have been summarized in systematic reviews and meta-analyses: these provide the strongest evidence for efficacy of interventions. Meta-analyses of these studies assess the strength of evidence present regarding diabetes prevention and they determined the effect size through a single summary estimate of the effect.

For lifestyle modification, recent meta-analyses have shown that this approach is associated with a 36–54% lower risk of progressing to type 2 diabetes compared to treatment after one year: 4% vs. 10%; RR 0.46 [95% CI 0.32, 0.66] and after three years: 14% vs. 23%, RR 0.64 [95% CI 0.53, 0.77] [25,26,27]. The mechanisms by which lifestyle modification approaches

work are diverse. Meta-analyses testing this approach show reduction in plasma glucose levels by effecting changes in the total energy intake of individuals at high risk for Type 2 diabetes. Significant improvement with lifestyle intervention (focusing on physical activity and exercise) on the risk factors like BMI and HbA1c was found in patients with type 2 diabetes[28]. These meta analyses also show that lifestyle intervention is more effective than the standard care regarding the glycaemic control of type 2 diabetic patients, particularly when there is a weight loss[29]. Another recent review by Kerrison *et al.*, evaluated the effectiveness of lifestyle adaptation in 9 RCTs. The cumulative incidence of diabetes ranged from 3.0% to 39.3% for the intervention group, with a mean value of 15.44% (across 8 studies). The cumulative incidence of diabetes for the control group ranged from 7.0% to 38.0%, with a mean value of 24.01%. Overall, cumulative incidence of diabetes was drastically reduced in the intervention groups compared to control groups with standard care[30].

Pharmacological interventions using different antidiabetic drugs, especially agents that improve insulin sensitivity, can prevent or at least slow the progression of prediabetes to diabetes. Randomized clinical trials included in systematic reviews conducted by by Gillies *et al.*[31], Yuen *et al.*[32], Balk *et al.*[33] aim to quantify the effectiveness of pharmacological and lifestyle interventions to prevent or delay type 2 diabetes in people with impaired glucose tolerance[31]. Existing meta-analyses show that certain classes of drugs can reduce the risk of type 2 diabetes and these include biguanides, Alpha-glucosidase inhibitors, Lipase inhibitors, DPP-4 inhibitors, Thiazolidinediones, GLP-1 receptor agonists, other agents like anti hypertensives (ACE inhibitors, Angiotensin II receptors), lipid lowering agents and hormone therapies that target underlying disease process of lipotoxicity and insulin resistance.

A meta-analysis by LeBlanc *et al.* reviewed a total of 122 RCTs (N = 62 533) and 2 observational studies (N = 209 993) to gather evidence on benefits and harms of behavioral and pharmacotherapy weight loss interventions in adults as part of the US Preventive Services Task Force. Participants with prediabetes in weight loss interventions had a lower risk of developing diabetes compared with controls (relative risk, 0.67 [95% CI, 0.51 to 0.89]). Behavior-based weight loss interventions with or without weight loss medications were associated with more weight loss and a lower risk of developing diabetes than control conditions[34]. Another meta analysis by Hemmingsen *et al.*, assessed the effects of insulin secretagogues on the prevention or delay of diabetes and its associated complications in people with impaired glucose tolerance, impaired fasting blood glucose, moderately elevated glycosylated haemoglobin A1c or any combination of these. Six RCTs with 10,018 participants was included in the analysis. Type 2 diabetes developed in 1674/4645 (36.0%) participants in the nateglinide group and in 1580/4661 (33.9%) in the placebo group (HR 1.07; 95% CI 1.00 to 1.15; P = 0.05; moderate-quality evidence). Authors concluded there was insufficient evidence to demonstrate whether insulin secretagogues when compared mainly to placebo reduced the risk of developing Type 2 diabetes and its associated complications in people at increased risk for the development of Type 2 diabetes[35].

The meta analysis provide evidence that the mechanisms by which medications work is by promoting weight loss and by improving insulin sensitivity. Pharmacological interventions cannot be considered as replacements of the benefits of diet and/or exercise but rather as an additional intervention with potential benefits and side effects.

Finally, meta-analyses testing supplements have mostly tested the use of vitamin and mineral supplements for the prevention of Type 2 diabetes is of increasing interest[36]. Vitamins and minerals are micronutrients which play diverse roles in the human body. They prevent deficiency diseases such as scurvy, pellagra, and rickets. They also regulate metabolism and gene expression and influence the development and progression of many chronic diseases[37]. The micronutrients in diabetes management include chromium, zinc, vitamin D, fibers and L-arginine[36].

A meta-analysis by Yeh *et al.* examined 18 clinical trials that evaluated the impact of vitamin and mineral supplements on diabetes management and development[38]. It was difficult to draw conclusions regarding efficacy because there were few trials per supplement. While no major safety concerns were reported in these trials, the trials were of poor design and data quality. Research on vitamin and mineral supplements has also been hindered by a lack of accurate and meaningful assays that detect functional micronutrient deficiencies. In the case of chromium, for instance, it is postulated that supplementation of targeted individuals might be more beneficial[39].

Purpose of the Current Study

The evidence based from existing meta-analysis shows lifestyle modification approaches, some pharmacotherapeutics and some dietary supplements reduced diabetes risk from 26% to 34%[32]. However, there is debate around which type of intervention has the largest impact in the short and long terms. Comparative effectiveness analyses are needed to determine which approach is more effective in people with prediabetes. The purpose of this systematic review and meta-analysis is to collate further evidence to answer this question. This is a rigorous,

comprehensive attempt made to evaluate randomized trials that incorporate non-surgical interventions and post-intervention follow-up periods along with reporting glucose measurements on a continuous scale as well as progression to Type 2 diabetes mellitus. The novelty of the present review is the inclusion of two new classes of drugs (GLP-1 and SGL-2 inhibitors) that are being tested for diabetes prevention. Systematic review and meta-analyses of randomized controlled trials provide the strongest evidence about treatment efficacy and are needed to inform future prevention programs and policies.

Methods

Overview

The objective of this systematic review and meta-analysis is to estimate the effects of diverse prevention interventions on global diabetes incidence. For this, I updated a previously published systematic review that included 55 randomized controlled trials (RCT) testing lifestyle modification interventions and pharmacotherapeutics for diabetes prevention. My thesis expands this review by including studies published after December 1st, 2014 and studies evaluating new lifestyle modification strategies, new pharmacotherapeutics, and new dietary supplements for diabetes prevention. In line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines,[40] this systematic review was conducted in four steps: (i) systematic literature search, (ii) removal of duplicate articles, (iii) identification of potentially relevant articles based on the title and abstract, and (iv) full-text screening.

Study Search and Selection

PICO framework which was designed to focus clinical questions and to prompt for publication type or type of question asked has been used to develop literature search strategies for this systematic review (Appendix 1)[41]. PICO stands for P atient problem, I ntervention, C omparison, and O utcome[42]. The PubMed electronic database was systematically searched for original peer-reviewed published articles in any language between December 1st 2014 and October 22nd 2019[43]. The search strategy was developed using database-specific controlled vocabularies, free-text terms and Medical Subject Headings (MeSH) terms without language restrictions[44].

Identified study titles were imported directly into a reference manager software (EndNote) and later to an online screening tool (Covidence)[45]. Eligible studies were randomized controlled trials (RCTs) testing any diabetes prevention intervention in adults (≥19 years of age) with prediabetes (defined by either impaired glucose tolerance (IGT), impaired fasting glucose (IFG), or both) that lasted at least 6 months and that reported diabetes incidence as the main outcome.

Screening and Data Extraction

Identified titles and abstracts were screened in Covidence by two independent reviewers. Covidence is a data management program for systematic reviews that allows for the management, screening and selection of articles. The full text potentially eligible studies were retrieved and two reviewers independently assessed full texts for eligibility. Inclusion decisions were compared and discrepancies were resolved by a third reviewer.

Data from eligible studies were extracted into a standardized excel file using a pre-defined list of variables. Diabetes incidence was the primary outcome of interest. Crude diabetes incidence numbers reported for both the intervention and control groups were extracted or calculated based on the number of participants who developed diabetes at the end of the study period. Data were also extracted on the characteristics of included studies (country, sample size, duration of intervention, total duration of the study) and the study population (age, gender, race, body mass index and weight loss).

Risk of Bias Assessment

Risk of bias across studies was assessed using the Cochrane Risk of Bias Assessment (version 2) tool which was released in August 2019 and is suitable for individually-randomized,

parallel-group trials[46]. The tool is a new research tool for assessing the risk of bias in randomized controlled trials based on five domains: randomization process, deviation from intended interventions, missing outcome data, measurement of the outcome and selection of the reported result. Signaling questions in each domain are factual in nature and they aim to elicit information related to each bias domain. There are 5 response options (yes, probably yes, probably no, no, no information) which are fed into algorithms that form judgments regarding the risk of bias. A proposed judgement about the risk of bias arising from each domain is generated by an algorithm, based on answers to the signaling questions. Domains and signaling questions are presented in Table 1.

Table 1: Domains of Cochrane Risk of Bias Assessment (Risk of Bias2) tool

Type of bias	**Description**	**Relevant domains in the Collaboration's 'Risk of Bias' tool**
Bias arising from the randomization process	Assessment of baseline imbalances to identify problems with the randomization process. For this systematic review, random sequence generation and concealment of allocation sequence was assessed between the intervention and control groups	Sequence generation Allocation concealment Baseline imbalances
Bias due to deviations from intended interventions	Evaluation of consistency between changes to intervention and the trial protocol. Assessments are categorized as per the intervention effect of interest - (1) the effect of assignment to the interventions at baseline ('intention-to-treat effect' (ITT)); or (2) the effect of adhering to intervention as specified in the trial protocol ('per-protocol effect'). All studies were classified into ITT or	Blinding of participants and personnel from intended interventions and outcome assessments Deviations due to trial context Deviations affecting the outcome Between group balance in deviations Appropriate analysis - estimate the effect of assignment Appropriate analysis - participants in randomized groups

	per protocol effect and assessed for bias	Balanced non-protocol interventions Factors affecting outcome - implementation, non-adherence Appropriate analysis - estimate the effect of adherence
Bias due to missing outcome data	Assessment of drop-outs during the study because this impacts the intervention effect estimate. So, all studies were assessed for participant absence as drop-outs/lost to follow-up or death, participant attendance for key study measurement visits, missing data during relevant visits, data loss/unavailability	Completeness of the outcome data Bias of results Treatment of missing data - true value assessment
Bias in measurement of the outcome	Assessment of the errors that can bias estimates of intervention effect containing measurement error, misclassification error, under-ascertainment or over-ascertainment. The studies were assessed for method of outcome measurement, the differences in measurement, the outcome assessor, blinding of the outcome assessor and if the outcome is likely to be influenced by knowledge of intervention received.	Outcome measurement - between groups, methodsBlinding of assessors to interventionAssessment - knowledge of intervention
Bias in selection of the reported result	Assessment of bias that arise due to the method of selection of the reported result (based on its direction, magnitude or statistical significance) from among multiple intervention effect estimates that were calculated by the trial investigators. The studies were evaluated for (i) selective reporting of a particular outcome measurement from multiple measurements assessed within an outcome domain; and (ii) selective reporting of a particular analysis from multiple analyses of a specific outcome measurement.	Analysis - adherence to prespecified plan Results selection - multiple outcome measurements, Multiple analysis of the data

Overall bias	Corresponds to the worst risk of bias in any of the domains	Overall predicted direction of bias for the outcome

The risk assessment tool requires a comparison between the pre-specified analysis intentions and the reported analyses in order to assess potential selection bias of multiple outcomes or endpoints. In case a preregistered analysis plan is met, 'low risk of bias' is assigned. 'High risk of bias' is assigned only if it is likely that reported outcomes have been selected based on the results, i.e. a deviation from the preregistered protocol is detected. If no information is available, Risk of Bias 2.0 suggests 'some concern'. Furthermore, in cases where pre-registration is lacking, Risk of Bias 2.0 suggests the methods section of an article is used as a source of the analysis intentions. Risk of Bias 2.0 tool provides a system-based algorithm result for the risk of bias judgment for each domain. The data from the Quality assessment summary generated by Risk of Bias 2.0 tool was extracted into a Cochrane data extraction excel file.

Data Analysis

Pairwise, random effect meta-analyses weighted by the inverse variance, were conducted. Pooled relative risks (RR) with 95 % confidence intervals, (95% CI), were estimated from the number of events in the intervention and control groups. A pooled relative risk was obtained separately for each intervention strategy tested: lifestyle, pharmacotherapeutics and dietary supplement groups. For trials that had more than one comparator to the intervention of interest, the arm whose procedures most resembled usual care or no intervention was chosen as the control arm.

Subgroup analysis and visualization of forest plot were used to explore heterogeneity in study effects, where within-study and between-study variations were examined. The I^2 statistic

was used to investigate heterogeneity in study effects[47], where values of 25 %, > 50 % and > 75 % were deemed as low, substantial and considerable degree of heterogeneity, respectively. Meta-regressions were conducted to explore the contribution of participant weight change on treatment effect heterogeneity.

Egger test and funnel plots were examined to assess publication bias[48,49]. The "trim and fill" method was used to examine the effect of missing studies with null findings on the pooled diabetes relative risk[50]. All analyses were performed using metafor package in R Version 2.1-0[51].

Results

Study characteristics

The search yielded 21,672 titles, of which 75 studies were eligible and included in the systematic review. The PRISMA flowchart reporting the study selection flow is presented in Appendix 2.

The 65 included studies for meta-analysis (Appendix 5) enrolled 147,001 participants (56,562 in intervention groups and 90,439 in control groups) and analyzed data from 125,483 participants (44,974 in intervention groups and 80,509 in the control groups). Characteristics of the 65 studies included in the systematic review and meta-analysis are presented in supplementary Appendix 3 - Table 2a and Table 2b. Participant mean age was 54.66 (SD 6.72) in the intervention and control groups. The intervention group and control group had 53.03% and 55.61% male participants, respectively. White/European participants were reported in 33 studies. Most of the studies (42%) were conducted in Asia, followed by 27.4% in Europe, 17.8% in North America, 1.6% in Oceania, and 11.3% in multiple countries. On an average, the interventions lasted 2.15 years (SD 1.57), with a mean duration of 3 years (SD 1.87), inclusive of follow-up phase.

Of the 65 studies included for meta-analyses, 31 studies tested lifestyle modification interventions (93.5% diet and physical activity modification and 6.5% diet modification only). These interventions were delivered via individual counseling, group education sessions, online education sessions, telephone-delivered messages, short message text services, and automated interactive voice response systems. Control groups received a combination of minimal diet and physical activity advice through group sessions or pamphlets less frequently. Pharmacotherapeutics were tested in 25 studies that included biguanides (7 studies), alpha-

glucosidase inhibitors (4 studies), meglitinides (2 studies), sulphonylurease (1 study), thiazolidinediones (2 studies), incretin mimetic (1 study), recombinant human insulin analog (1 study), anti-hypertensive studies reported the usage of ACE inhibitors (1 study), and angiotensin II receptor blocker (2 studies). Dietary supplements tested in 9 studies included Vitamin D (4 studies), L-arginine (2 studies) and fiber, chromium and zinc (1 study each). The control group received general advice for lifestyle changes or observation only or standard of care treatment or placebo.

Risk of bias

Studies were grouped under Intention to Treat (46 studies – 19 studies in the lifestyle modification group, 21 studies in the pharmacotherapeutics group and 6 studies in the supplement group) or Per-Protocol analysis (19 studies – 11 in the lifestyle modification group, 6 in the pharmacotherapeutics group and 2 in the supplement group). The risk of bias assessment results for intention to treat studies and per protocol effect studies are presented in Appendix 4a and 4b. The reviews for 3.1% randomized trials were rated as overall high risk, reviews for 78% randomized trials carried overall low risk and the remaining 18.5% randomized trials were assessed to have some concerns as overall risk.

Domain wise, high risk of bias was seen in 1.5% studies as deviations from intended interventions and 9.2% studies as measurement of the outcome. Some concerns with risk of bias was expressed in 18.5% studies in the randomization process. The other 12.3% of the studies where some concerns were risk of bias was expressed was related to deviations from intended interventions and measurement of the outcome. The justification for high risk of bias and for risk of bias with some concerns were mainly due to allocation concealment and random sequence generation along with the possibility of selective reporting, which was examined and compared

to guidance provided in the Cochrane handbook[52]. Also, for high risk of bias, all outcomes were not reported and the handling of missing values was not explained adequately. Discrepancies have been reported descriptively. For lifestyle intervention studies, allocation concealment may not be possible because the type of intervention is obviously known to both the health care providers and the participants. Successful and complete blinding (that is, blinding of participants, caregivers and outcome assessors) is often difficult to achieve and generally not feasible in evaluating lifestyle interventions. Participants in lifestyle interventions are actively involved in the intervention, precluding adequate blinding. For example, someone running, cycling or practicing yoga will know that they are doing that activity[53].

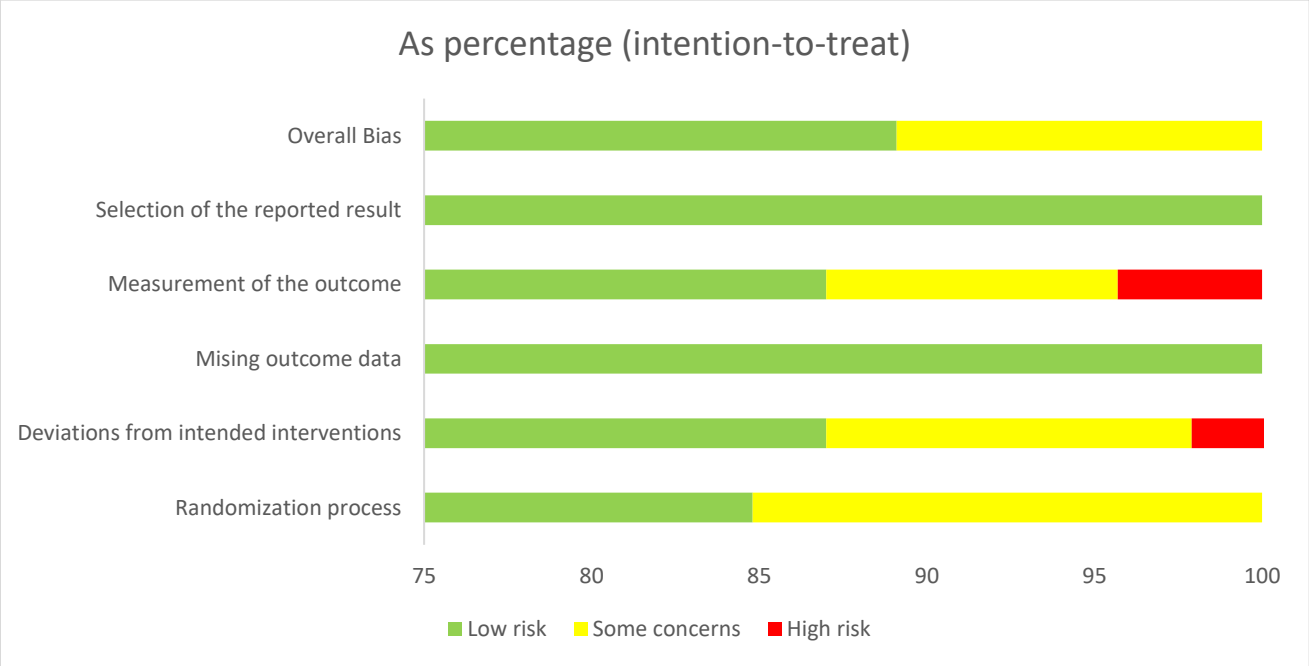


Figure 1.a: Risk of Bias assessment results. Panel A: Risk of bias assessment for "intention to treat" group, 'green' means low bias, 'red' means high bias, 'yellow' means some concerns.

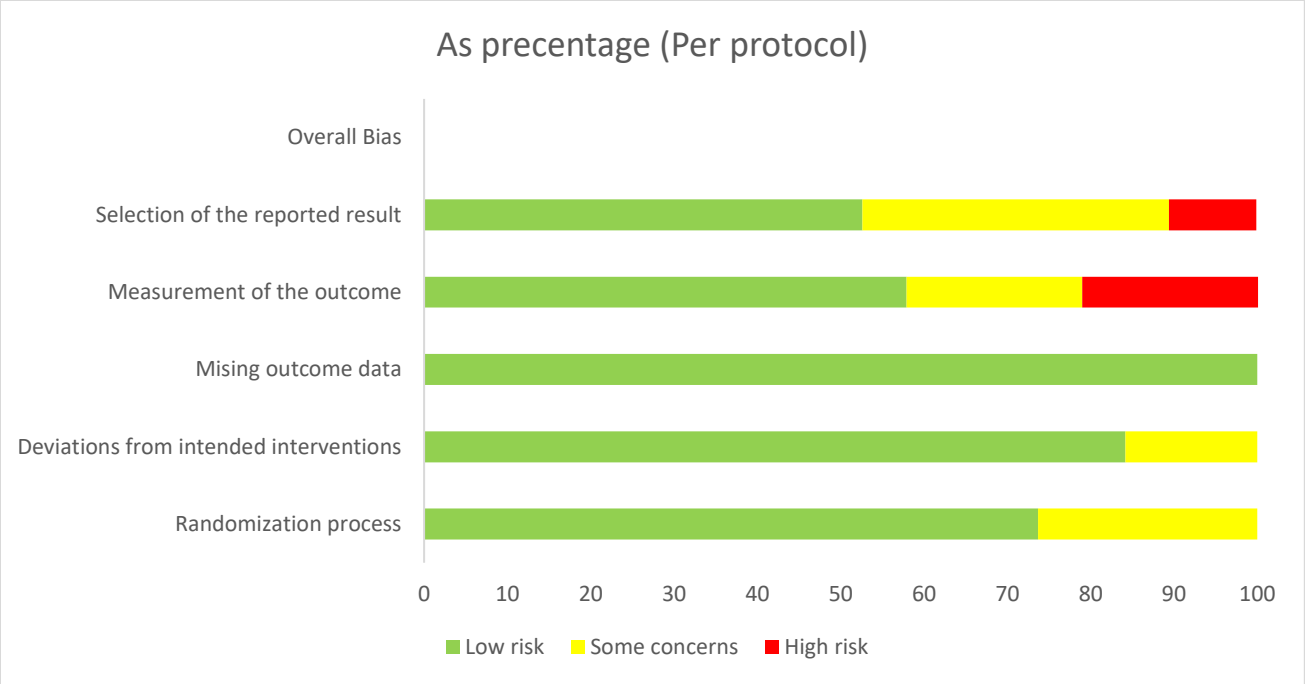
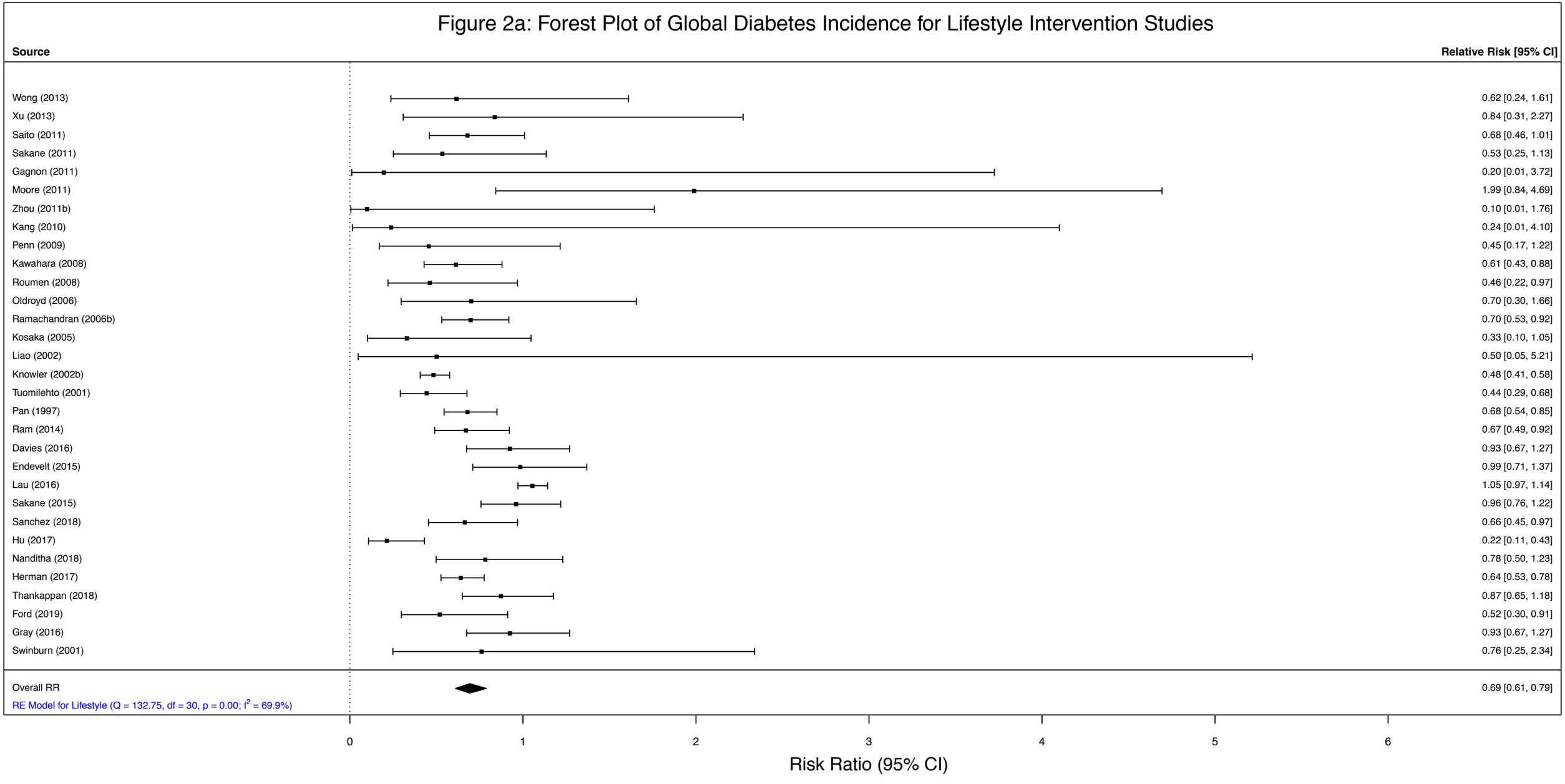


Figure 1b: Risk of Bias assessment results. Panel B: Risk of bias assessment for "per protocol effect" group, 'green' means low bias, 'red' means high bias, 'yellow' means some concerns.

Diabetes incidence

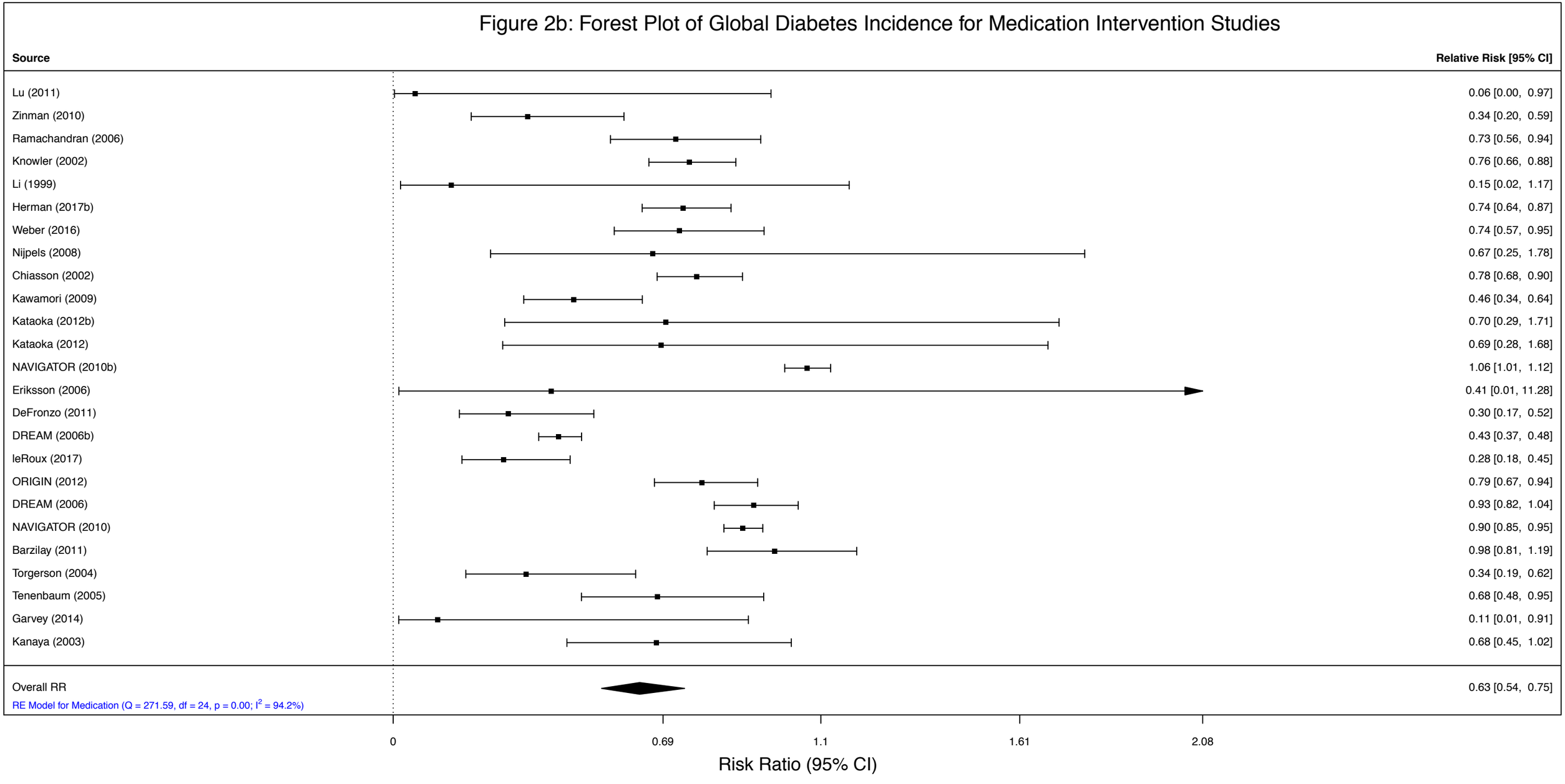
The effects of interventions on diabetes incidence was investigated in 65 studies according to intervention strategy. There were 31 studies testing lifestyle modification interventions among 74,162 participants. Interventions lasted 1.83 years (SD 1.35) and the follow-up duration was for 2.8 years (SD 1.93). Participants receiving a lifestyle modification intervention had a 31% lower risk of progressing to diabetes than control participants at the end of the study duration (RR= 0.69 [95% CI 0.61, 0.79], Figure 2a). These studies showed considerable heterogeneity ($Q = 132.75$, $I^2 = 69.9\%$, $p < 0.001$). A meta-regression including participant weight loss during the lifestyle intervention in 33 studies explained 68.3%, of this heterogeneity ($R^2 = 68.27\%$, $p=0.0014$). In this model, each additional kilogram of weight lost associated with 10% additional reduction in diabetes risk ($\beta = -0.0981$, $p = 0.0014$).

Figure 2a: Forest Plot of Global Diabetes Incidence for Lifestyle Intervention Studies



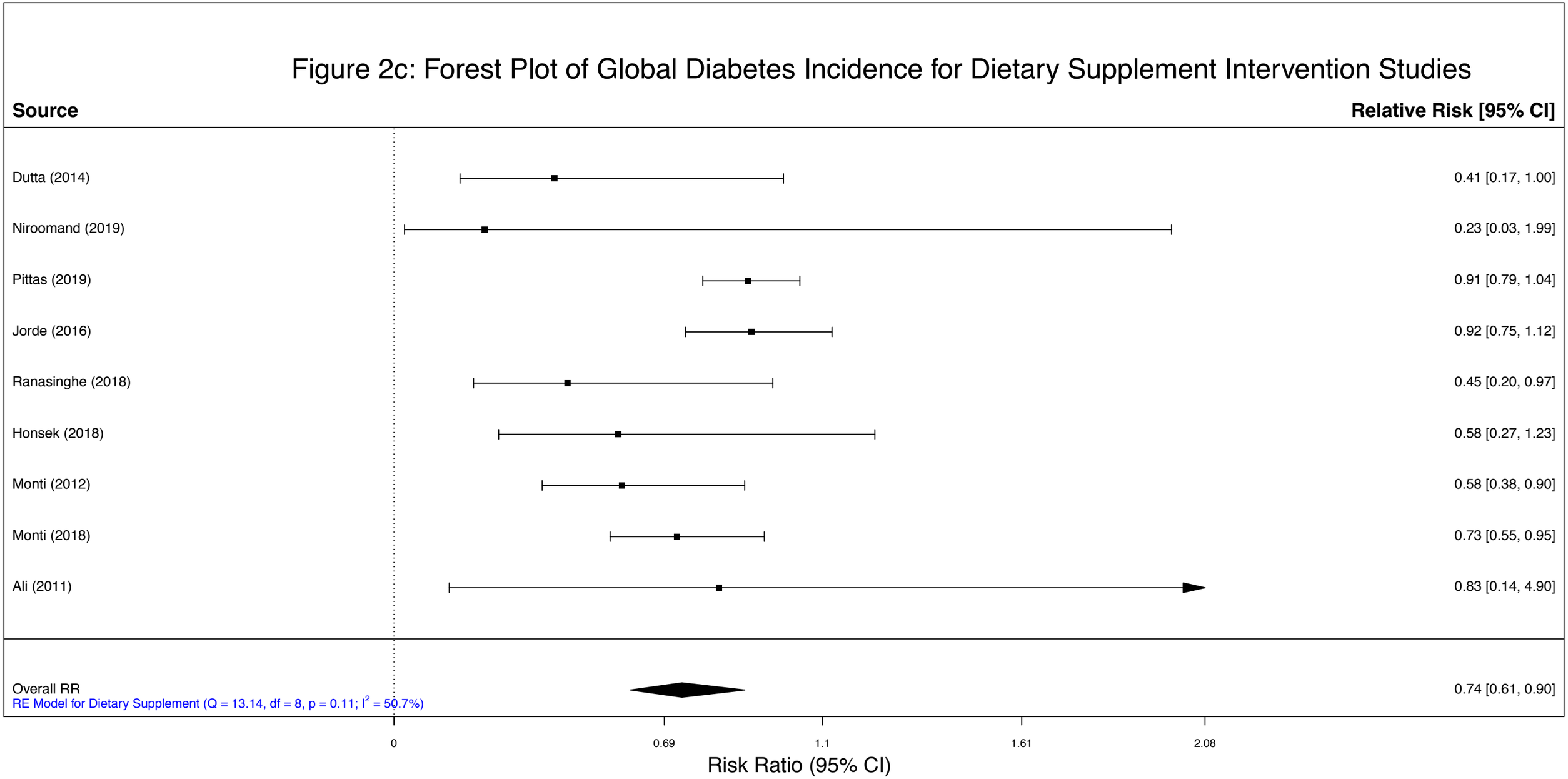
There were 25 studies testing pharmacotherapeutics interventions among 48,047 participants. Pharmacotherapeutics interventions lasted 2.64 years (SD 1.72) and the follow-up duration was for 3.2 years (SD 1.46). Participants receiving a pharmacotherapeutics modification intervention had a 37% lower risk of progressing to diabetes than control participants at the end of the study duration (RR= 0.63 [95% CI 0.54, 0.75], Figure 2b). The studies showed considerable heterogeneity ($Q = 271.59$, $I^2 = 94.2\%$, $p < 0.001$). A meta-regression including participant weight loss during the pharmacotherapeutics intervention in 10 studies explained 17% of this heterogeneity (R^2=16.78%, p=0.0877). In this model, amount of weight loss associated with 7.5% additional reduction in diabetes risk ($\beta = 0.0755$, $p = 0.0877$).

Figure 2b: Forest Plot of Global Diabetes Incidence for Medication Intervention Studies



There were 9 studies testing dietary supplement interventions among 3,709 participants. On an average, dietary supplement interventions lasted 1.92 years (SD 1.7) and the follow-up duration was for 3.1 years (SD 2.7). Participants receiving a dietary supplement modification intervention had a 26% lower risk of progressing to diabetes than control participants at the end of the study duration (RR=0.74 [95% CI 0.61, 0.74], Figure 2c). The studies showed substantial heterogeneity ($Q = 13.14$, $I^2 = 50.7\%$, $p > 0.001$). A meta-regression including participant weight loss during the dietary supplement intervention was performed and the model fit the data poorly. This is owed to the lower number of studies being analyzed (i.e less than 10), where 5 studies reported the weight change. Again, a meta-regression including total duration of the supplement intervention in 9 studies could not be conducted because the model fit the data very poorly. We required more than 10 studies to fit the model to this data.

Figure 2c: Forest Plot of Global Diabetes Incidence for Dietary Supplement Intervention Studies



Assessment of publication bias

Egger test ($t = -5.1541$, $df = 63$, $p < .0001$) and funnel plots suggested there is publication bias, meaning small studies with null effects were less likely to be published. The trim and fill test showed 8 studies with null effects were missing for lifestyle modification, 3 studies for pharmacotherapeutics, and 4 studies for dietary supplement intervention. If included, the observed pooled effects would have been RR=0.75 ([95% CI 0.66, 0.87]) for lifestyle, RR=0.65 ([95% CI 0.55, 0.77]) for meds and RR=0.82 ([95% CI 0.70, 0.96]) for supplements (Figures 3a, 3b, 3c).

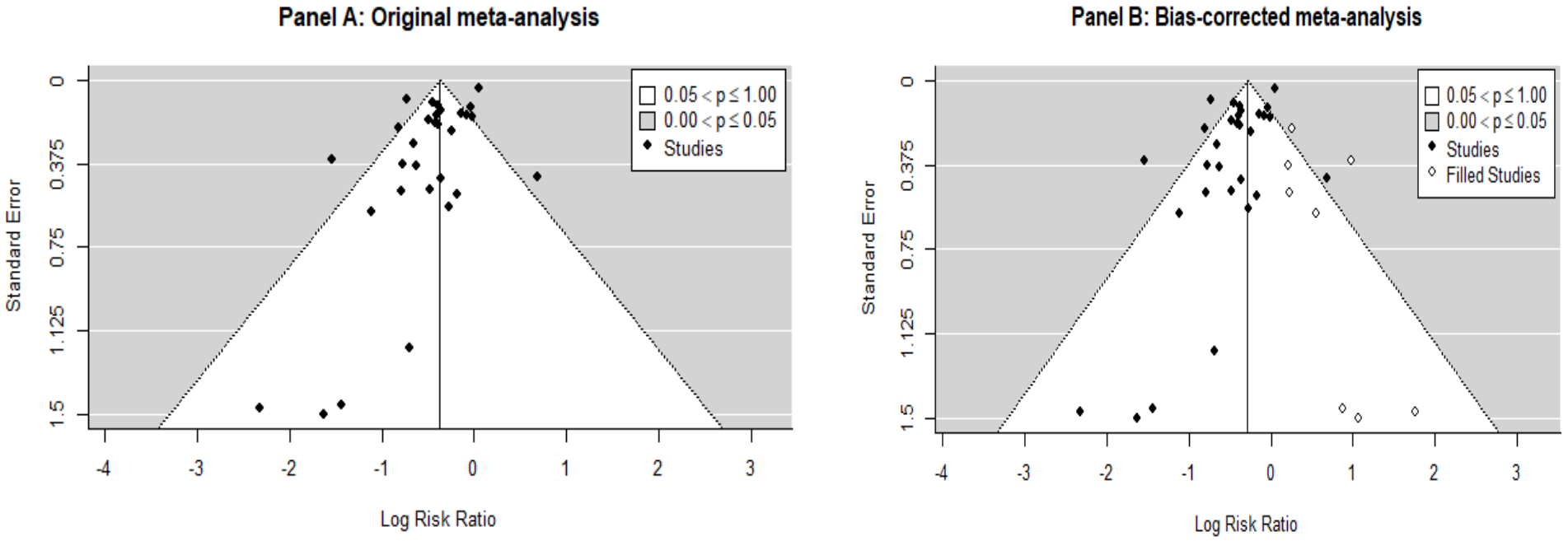


Figure 3a: Funnel plot of the meta-analysis of Lifestyle modification intervention studies before (Panel A) and after (Panel B) applying the Trim-and-fill method. The closed dots indicate the observed studies, and the open dots indicate the missing studies imputed by the trim-and-fill method (based on the estimator L0). The dashed lines that create a triangular area indicate the 95% confidence limits (under the random-effect setting), and the vertical solid line represents the overall effect size.

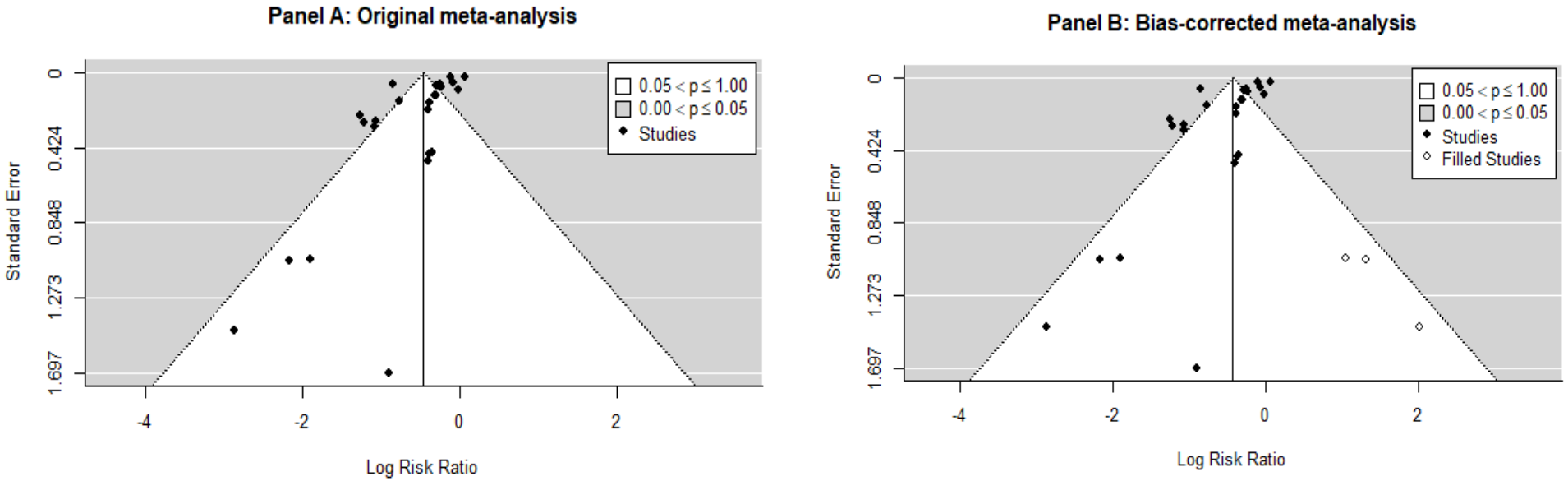


Figure 3b: Funnel plot of the meta-analysis of Pharmacotherapeutic intervention studies before (Panel A) and after (Panel B) applying the Trim-and-fill method. The closed dots indicate the observed studies, and the open dots indicate the missing studies imputed by the trim-and-fill method (based on the estimator L0). The dashed lines that create a triangular area indicate the 95% confidence limits (under the random-effect setting), and the vertical solid line represents the overall effect size.

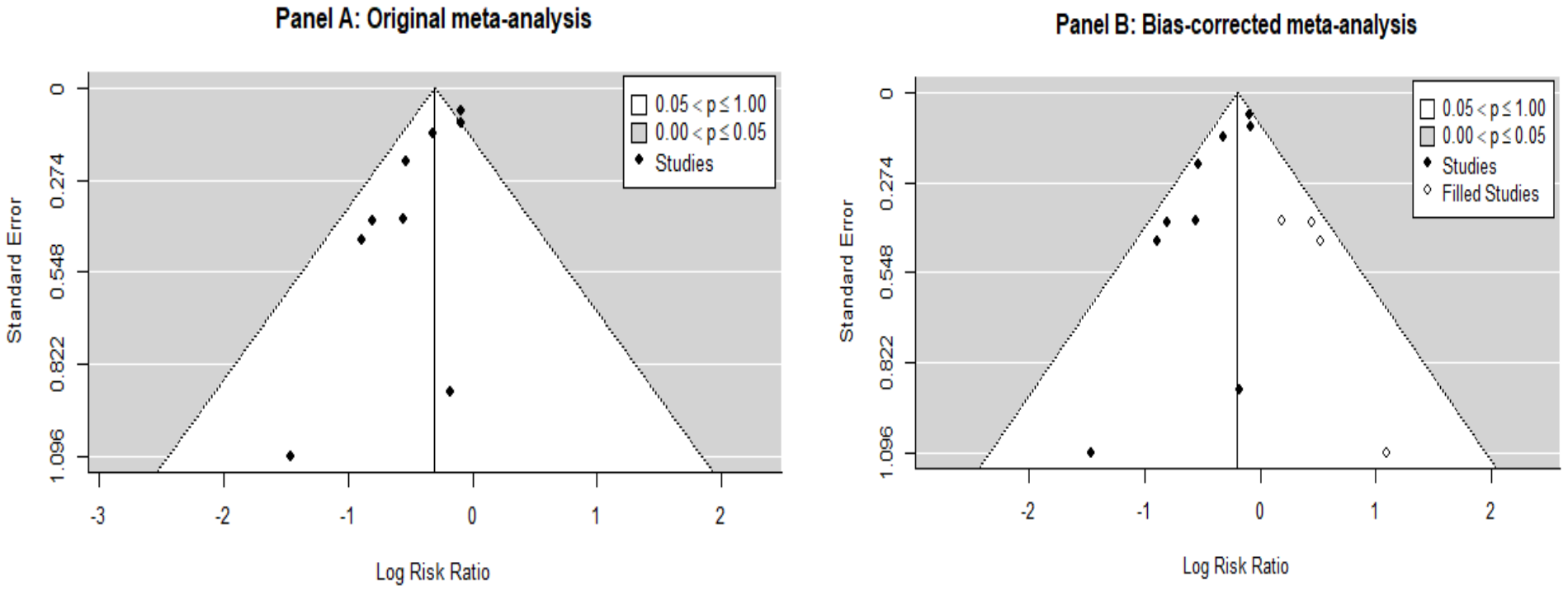


Figure 3c: Funnel plot of the meta-analysis of dietary supplement intervention studies before (Panel A) and after (Panel B) applying the Trim-and-fill method. The closed dots indicate the observed studies, and the open dots indicate the missing studies imputed by the trim-and-fill method (based on the estimator L0). The dashed lines that create a triangular area indicate the 95% confidence limits (under the random-effect setting), and the vertical solid line represents the overall effect size.

Discussion

Summary

The objective of this study was to summarize the evidence around diverse diabetes prevention approaches globally. The evidence collated through this systematic review and meta-analysis of 65 randomized controlled trials involving 147,001 participants with prediabetes showed that lifestyle modification, pharmacotherapeutic approaches and dietary supplements reduced the risk of type 2 diabetes by 31%, 37% and 26% respectively. Weight loss seems to play a role in reduction of diabetes risk in lifestyle modification and pharmacotherapeutics approaches. Both lifestyle modification interventions and pharmacotherapeutic interventions seem to be equally effective in diabetes risk reduction. More evidence is required to evaluate diabetes risk reduction through dietary supplements intervention.

Recent meta-analyses of randomized controlled trials have shown lifestyle modification strategies that focus on increasing physical activity and improving diets reduce diabetes risk by 33% to 40%, which aligns with our estimates. Previous systematic reviews have found that sustained reduction of Type 2 diabetes could be a result of the lifestyle changes[54,23,55,56]. In addition to these meta analyses, the research study by Glechner et al., showed a 36–54 percent lower risk of progressing to type 2 diabetes compared to treatment as usual (after one year: 4% vs. 10%; RR 0.46 [95% CI 0.32, 0.66]; after three years: 14% vs. 23%, RR 0.64 [95% CI 0.53, 0.77]) after one and three years of lifestyle intervention[25,26,27]. Another recent study by Kerrison et al., showed cumulative incidence of diabetes ranged from 3.0% to 39.3% for the intervention group, with a mean value of 15.44% (across 8 studies). The cumulative incidence of diabetes for the control group ranged from 7.0% to 38.0%, with a mean value of 24.01%. Overall, cumulative incidence of diabetes was drastically reduced in the intervention groups compared to control

groups (standard care)[30]. The relative risk (RR) reported through this meta-analysis is consistent with the results reported in previous studies because the same set of studies have been included in the meta analysis and the new studies that are included follow the design of big randomized clinical studies like DPP and Da Qing.

For the pharmacotherapeutic interventions, findings from this meta-analysis are consistent with the results reported in previous studies. A meta-analysis from the US Preventive Services Task Force found weight loss medications reduced diabetes risk by 33% among people with prediabetes. Findings from another study by Hemmingsen et al., supports the results from the current study where the effects of insulin secretagogues on the prevention or delay of T2DM and its associated complications in people with impaired glucose tolerance, impaired fasting blood glucose, moderately elevated glycosylated haemoglobin A1c (HbA1c) or any combination of these, was evaluated. The systematic reviews by Stevens et al.[57] and Merlotti et al.[58] quantified the lifestyle and medication intervention like the previous studies but also evaluated the effectiveness of surgical interventions in reducing the progression to Type 2 diabetes mellitus in people with IFG or IGT. The results of the pharmacotherapeutics intervention provide further evidence to support our current results for the pharmacotherapeutic group.

This meta-analysis is the first to obtain pooled effects for dietary supplements; we found supplements reduce diabetes risk by 26%. To our knowledge, there is only one existing meta-analysis that has explored the effects of vitamin and mineral supplements but authors could not draw conclusions regarding efficacy of these supplements because there were few trials available[38]. Randomized controlled trials have not clearly demonstrated the effects of vitamin D in the prevention or treatment of diabetes. The quality of the articles included did not

demonstrate low risk of bias either. Therefore, this meta-analysis is the first to provide evidence of the potential of dietary supplements for diabetes prevention and our findings suggest that dietary supplements are promising but confirmation from other meta-analyses is warranted.

We found every kilogram of weight loss was associated with an additional 10% and 7.5% decrease in risk of progression to diabetes in the lifestyle modification approaches and pharmacotherapeutics, respectively. Variable effects of weight loss like positive and null effects on diabetes incidence have been shown by other systematic reviews and meta analyses[31,33,58]. This can be due to differences in characteristics across the studies included in the present analysis (i.e. race, age, level of risk prior to intervention), type of interventions, intensity of interventions, combination of the interventions, duration of the intervention and follow-ups, method of delivery of the interventions, or time period in which the intervention took place. Despite this, weight loss is consistently associated with greater risk reduction and our findings align with these observations.

Strengths

An extensive literature review was performed for published peer reviewed journal articles following randomized controlled study designs and using comprehensive search criteria. Randomized controlled trials are the gold standard for assessing an intervention, with non-randomized studies having a greater potential for bias. This meta analysis includes a wide range of global studies that met the inclusion criteria. Since 78.5% of the studies were deemed as having overall low risk of bias, these findings provide an unbiased estimate of diabetes risk reduction.

Limitations

High levels of heterogeneity were found in the outcome assessed. Heterogeneity is a statistical measure of how much variability there is between study effects and whether this is more than one would expect by chance. Heterogeneity was partially explained through subgroup analyses and meta regression in the current analysis. Many specific factors regarding the intervention and participant population were assessed to provide a thorough overview of which factors and in which populations prevention interventions are the most efficacious.

The diabetes prevention interventions assessed are complex interventions and therefore it might not be possible to elucidate what constitutes an effective program through the use of subgroup analyses alone. As the subgroup analyses conducted assessed weight change in isolation, it may be that combinations of factors are important and that we cannot assume independence of factors on the outcome. Bivariate meta-regressions were conducted where the effects of weight change alone cannot be attributed towards the diabetes risk reduction. Extending the meta-regression analysis to incorporate multiple factors, is needed to fully explain the heterogeneity seen. The efficacy of lifestyle modification intervention was not directly compared with that of pharmacotherapeutics or supplements, so we cannot truly determine which, among these approaches is most effective. The search terms used were in the English language and studies may have been missed if they were published in other languages.

In the current analysis, a sub group analysis was not done for each class of pharmacotherapeutics. Conclusions could not be drawn for specific class of pharmacotherapeutics. Specifically, for the three studies that used weight loss medications as interventions, evidence is unavailable in terms of past systematic reviews and meta data analysis. Requirement of further studies is indicated to evaluate the long-term effects of weight loss

medications on both weight lost and weight regained and their effects on future diabetes incidence.

Conclusion

This systematic review and meta-analysis of randomized controlled trials shows pharmacotherapeutics, lifestyle modification and dietary supplements can significantly reduce the progression to Type 2 diabetes in those populations at risk. The evidence provided here may guide the health care professionals to individualize preventive care appropriate to community resources, individual motivations and coverage for various interventions. The results of this systematic review and meta analysis affirms the current evidence available and informs the design of future effectiveness trials. Researchers building pragmatic diabetes prevention programs are recommended to consider additional evidence regarding the role of dietary supplements in diabetes risk reduction. Higher quality of dietary supplement studies will encourage reviewers to add them in their analysis. Multi-faceted national level diabetes prevention programs are encouraged to be rolled out to reduce the disease burden and improve the clinical and economic outcomes for all persons who have, or are at risk for, diabetes.

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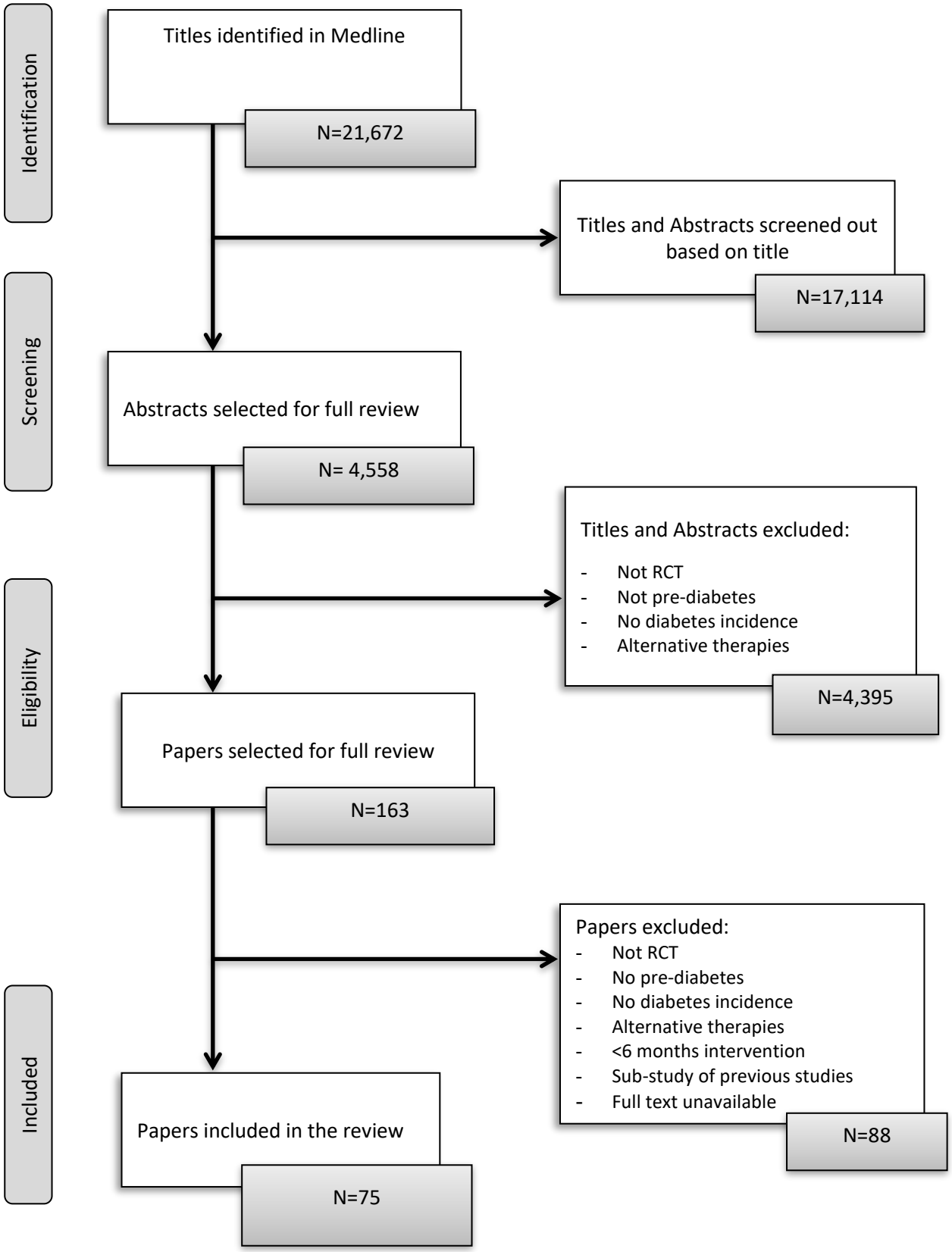
Appendix 1. PICO Framework for search strategy

Method	Efficacy Systematic Review and Meta-Analysis	
Databases Searched	MEDLINE	
Publication Dates	Articles Published and Indexed December 01, 2014 - October 22, 2019	
Search Terms and Dates	Combinations of medical subject headings and search terms, such as, *pre-diabetes*, *primary prevention* and *risk reduction*. Initial search conducted February 20, 2015, and updated search performed October 22, 2019	
Inclusion Criteria for Study Selection (PICOS)	Population	Adults (atleast 18 years old) with pre-diabetes, defined by either impaired glucose tolerance (IGT), impaired fasting glucose (IFG), or both
	Intervention	Efficacy of diabetes interventions lasting atleast 6 months
	Comparator	Between-group differences
	Outcome(s)	Diabetes incidence rates at the end of active interaction
	Study design	Randomized control trials
Quality Metrics	Bias arising from the randomization process:	
	Bias due to deviations from intended interventions	
	Bias due to missing outcomes data	
	Bias in measurement of the outcome	
	Bias is selection of the reported result	
	Overall Bias	

Appendix 2. Study screening and selection flow-diagram



Appendix 3. Supplement Table 1 – Baseline Characteristics

Supplement Table 2a. Baseline participant and intervention characteristics for included studies.

Included in Systematic Review and Meta-Analysis (n=147001)													
Author (year) Country	Participant Characteristics										Intervention Characteristics		
	N enrolled		Age (years)		Male %		BMI		Weight		Duration of Intervention (years)	Treatment tested	Mean Follow-up
	I	C	I	C	I	C	I	C	I	C			
Wong (2013) (1) China	54	50	54.1	55.2	90.7	96	25.55	26.25	69.49	72.32	2	Lifestyle	2
Xu (2013) (2) China	46	42	60.35	56.55	19	23	26.8	25.7	68.24	69.69	1	Lifestyle	1
Saito (2011) (3) Japan	311	330	50	48	72	71	26.9	27.1	74.1	74.8	3	Lifestyle	3
Sakane (2011) (4) Japan	146	150	51	51	50	49.3	24.8	24.5	64.9	63.9	3	Lifestyle	3
Gagnon (2011) (5) Canada	22	26	54.8	58.4	40.9	50	34.1	36	91.4	100.4	1	Lifestyle	1
Moore (2011) (6) Australia	208	99	63		41		29.66	29.79	80.7	82.02	0.5	Lifestyle	0.5
Zhou (2011b) (7) China	59	58	57	58.1	19	32.7	24.8	24.8			0.5	Lifestyle	0.5
Kang (2010) (8) Korea	25	75	45.84	47.47	100	100	26.77	25.6	77.48	75.17	2	Lifestyle	2
Penn (2009) (9) UK	51	51	56.8	57.4	41.2	39.2	34.1	33.5	93.4	90.6	3	Lifestyle	3
Kawahara (2008) (10) Japan	143	142	52.6	51.8	46	47.8	24.7	24.7	65.7	65.5	3	Lifestyle	3.1
Roumen (2008) (11) Netherlands	74	73	54.2	58.4	51	50.6	29.6	29.2	87.5	83	3	Lifestyle	3
Oldroyd (2006) (12) UK	37	32	58.2	57.5	46	68.7			85.3	85.5	0.5	Lifestyle	2
Ramachandran (2006b) (13) India	133	136	46.1	45.2	78	76.4	25.7	26.3	109		3	Lifestyle	2.8
Kosaka (2005) (14) Japan	102	356			100	100	24	23.8			4	Lifestyle	4
Liao (2002) (15) US	32	32	55.8	52.2	37	63	25.6	26.6	66.1	69.7	2	Lifestyle	2
Knowler (2002b) (16) US	1079	1082	50.6	50.3	34.5	31	33.9	34.2	94.1	94.3	0.5	Lifestyle	2.8
Tuomilehto (2001) (17) Finland	265	257	55	55	34	31.5	31.3	31			4	Lifestyle	6
Pan (1997) (18) China	438	133	44.4	46.5	56	54.8	26.3	26.2			6	Lifestyle	6
Ram (2014) (19) India	271	266			100	100					2	Lifestyle	2
Davies (2016) (20) UK	447	433	63.9	63.9	63.1	64.2	32	33.1	89.9	94.4	2	Lifestyle	3
Endevelt (2015) (21) Israel	111	112	51.9	55.4	53.3	59.2	29.8	30.8			0.5	Lifestyle	2
Lau (2016) (22) Denmark	11629	47987			49.8	48.9					0.5	Lifestyle	10
Sakane (2015) (23) Japan	1240	1367	48.9	48.9	82.5	84.1	24.4	24.3			1	Lifestyle	4
Sanchez (2018) (24) Spain	454	634	59.3	59.3	33.5	42	80.8	82.9	66.5	58	1	Lifestyle	2

Hu (2017) (25) China	214	220	69.2	69.5	43.5	39.5	23.5	23.9	59.5	59.7	0.75	Lifestyle	1
Nanditha (2018) (26) India	271	266	45.9	46.1	100	100	25.8	26.1			2	Lifestyle	5
Herman (2017) (27) US	1079	1073	50.6	50.9	32	33.65	33.9	33.9	94.3	94.4	0.5	Lifestyle	3
Thankappan (2018) (28) India	500	507	46.2	45.7	52.2	53.4			62.6	64.5	1	Lifestyle	2
Ford (2019) (29) India	283	295	45.1	44.2	59.6	59.6	27.8	27.9	74.5	74.4	0.5	Lifestyle	1
Gray (2016) (30) UK	447	433									2	Lifestyle	3
Swinburn (2001) (31) New Zealand	66	70	52.5	52	68	80	29.08	29.17	85.46	84.33	1	Lifestyle	1
Lu (2011) (32) China	106	86	62	64.72	53	52.3	27.1	26.92	72.2	71.45	2	Medication	2
Zinman (2010) (33) Canada	103	104	50	55	35	31.7	31.1	32	89.9	86.3	3.9	Medication	3.9
Ramachandran (2006) (13) India	133	136	46.1	45.2	81	76.4	25.7	26.3	94.3		3	Medication	2.5
Knowler (2002) (16) US	1073	1082	50.9	50.3	34	31	33.9	34.2	94.3	94.3	0.5	Medication	2.8
Li (1999) (34) China	45	33	49	50	65	70.2	26.4	26	10.34		1	Medication	1
Herman (2017b) (27) US	1073	1082	50.9	50.3	33.65	31	33.9	34.2	94.4	94.5	0.5	Medication	3
Weber (2016) (35) India	283	295	44.8	44	64	62.5	27.9	27.8	74.6	74.7	0.5	Medication	3
Nijpels (2008) (36) Netherlands	60	58	58.5	56.5	50.8	50	28.4	29.5	83.3		3	Medication	3
Chiasson (2002) (37)	714	715	54.3	54.6	48	50	31	30.9	87.6	87.1	3.3	Medication	3.3
Kawamori (2009) (38) Japan	897	883	55.7	55.7	60	60	25.76	25.89	94.9		0.9	Medication	3
Kataoka (2012b) (39) Japan	100	57	65	65	87	86	24.6	24.4			1	Medication	1
Kataoka (2012) (30) Japan	101	57	64	65	86	86	23.8	24.4			1	Medication	1
NAVIGATOR (2010b) (40)	4645	4661	64	63.8	49	49.7	30.5	30.5	83.6	83.6	5	Medication	5
Eriksson (2006) (41) Finland	17	17	58	53	12	58.8	27.9	28.8	91.4		0.5	Medication	1.5
DeFronzo (2011) (42) US	308	299	53	51.5	42	42	33	34.5	110.4		3	Medication	2.4
DREAM (2006b) (43)	2635	2634	54.6	54.8	42	39.9	30.8	31	84.8	85	3	Medication	3
leRoux (2017) (44) Denmark	1505	749	47.5	47.3	24	23	38.8	39	107.5	107.9	3	Medication	3.3
ORIGIN (2012) (45)	6300	6312	63.7	63.5	66.8	63.3	29.8	29.9	83.3	83.1	6.2	Medication	6.2
DREAM (2006) (43)	2623	2646	54.7	54.7	40	41.3	30.9	30.9	84.8	85	3	Medication	3
NAVIGATOR (2010) (40)	4631	4675	64	63.8	50	49.7	30.4	30.6	83.5	83.8	5	Medication	5
Barzilay (2011) (46)	3488	1762	66.9	67.1	60.6	60.9	27.6	27.5	83.5		4.7	Medication	4.7
Torgerson (2004) (47) Sweden	1655	1637	43	43.7	44.8	44.7	37.3	37.4	110.4	110.6	4	Medication	4
Tenenbaum (2005) (48) Israel	178	161	59.6	58.5	84	86	32.2	32.7	91.4	92.2	5	Medication	6.3
Garvey (2014) (49) US	295	159	51.3	52.5	36	36.5	36.3	36.1	103.4	102.9	2	Medication	2
Kanaya (2003) (50) US	1380	1383	67	67	0	0	28.6	28.5			1	Medication	4.1

Dutta (2014) (51) India	68	57	48.37	47.4	36.76	45.61	26.32	26.83			0.5	Supplement	2.3
Niroomand (2019) (52) Iran	81	81	45	48	63	61	31	32	82	85	0.5	Supplement	0.5
Pittas (2019) (53) US	1211	1212	59.6	60.4	55.3	55	32	32.1			4.5	Supplement	4.5
Jorde (2016) 54) Norway	278	278	62.3	61.9	62.9	60	30.1	29.8			5	Supplement	5
Ranasinghe (2018) (55) Srilanka	100	100	51.9	51.7	43	43	25.5	24.6			1	Supplement	1
Honsek (2018) (56) Germany	89	91	59	60	26	41	31.8	33	88.1	92.3	2	Supplement	2
Monti (2012) (57) Italy	66	68	57.2	58.2	58.3	54.16	30.4	29.5	84	82.3	1.8	Supplement	2.5
Monti (2018) (58) Italy	72	72							88.2	82.8	1.5	Supplement	9
Ali (2011) (59) US	12	10									0.5	Supplement	1

*If a study presented more than two intervention groups, then the study is listed twice with a letter (a or b) to designate the group.
I = Intervention Group C = Control Group

Supplement Table 2b. Risk of bias assessment and scores for each study

Included in Systematic Review and Meta-Analysis (n=147001)						
Author (year) Country	**Quality Scores**					
	Randomization process	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported result**	**Overall Bias**
Wong (2013) (1) China	Low	Low	Low	Low	Low	Low
Xu (2013) (2) China	Some concerns	Low	Low	High	Low	Some concerns
Saito (2011) (3) Japan	Low	Low	Low	Some concerns	Low	Low
Sakane (2011) (4) Japan	Low	Some concerns	Low	Low	Low	Low
Gagnon (2011) (5) Canada	Some concerns	Low	Low	Low	Low	Low
Moore (2011) (6) Australia	Low	Low	Low	Low	Low	Low
Zhou (2011b) (7) China	Low	High	Low	Some concerns	Low	Some concerns
Kang (2010) (8) Korea	Low	Some concerns	Low	High	Low	Some concerns
Penn (2009) (9) UK	Some concerns	Low	Low	Low	Low	Low
Kawahara (2008) (10) Japan	Low	Low	Low	Low	Low	Low
Roumen (2008) (11) Netherlands	Low	Some concerns	Low	Low	Low	Low
Oldroyd (2006) (12) UK	Low	Low	Low	Low	Low	Low
Ramachandran (2006b) (13) India	Some concerns	Low	Low	High	Low	High
Kosaka (2005) (14) Japan	Some concerns	Low	Low	Some concerns	Low	Some concerns
Liao (2002) (15) US	Some concerns	Some concerns	Low	High	Low	Some concerns
Knowler (2002b) (16) US	Low	Low	Low	Low	Low	Low
Tuomilehto (2001) (17) Finland	Low	Low	Low	Some concerns	Low	Low
Pan (1997) (18) China	Some concerns	Some concerns	Low	Some concerns	Low	Some concerns
Ram (2014) (19) India	Some concerns	Low	Low	High	Low	High
Davies (2016) (20) UK	Low	Low	Low	Low	Low	Low
Endevelt (2015) (21) Israel	Some concerns	Some concerns	Low	High	Low	Some concerns
Lau (2016) (22) Denmark	Low	Low	Low	Low	Low	Low
Sakane (2015) (23) Japan	Low	Low	Low	Low	Low	Low
Sanchez (2018) (24) Spain	Low	Low	Low	Low	Low	Low
Hu (2017) (25) China	Low	Low	Low	Low	Low	Low
Nanditha (2018) (26) India	Low	Low	Low	Low	Low	Low

Herman (2017) (27) US	Low	Low	Low	Low	Low	Low
Thankappan (2018) (28) India	Low	Low	Low	Low	Low	Low
Ford (2019) (29) India	Low	Low	Low	Low	Low	Low
Gray (2016) (30) UK	Low	Low	Low	Low	Low	Low
Swinburn (2001) (31) New Zealand	Low	Low	Low	Some concerns	Low	Some concerns
Lu (2011) (32) China	Low	Low	Low	Some concerns	Low	Some concerns
Zinman (2010) (33) Canada	Low	Low	Low	Low	Low	Low
Ramachandran (2006) (13) India	Some concerns	Low	Low	Some concerns	Low	Some concerns
Knowler (2002) (16) US	Low	Low	Low	Low	Low	Low
Li (1999) (34) China	Low	Low	Low	Low	Low	Low
Herman (2017b) (27) US	Low	Low	Low	Low	Low	Low
Weber (2016) (35) India	Low	Low	Low	Low	Low	Low
Nijpels (2008) (36) Netherlands	Low	Low	Low	Low	Low	Low
Chiasson (2002) (37)	Low	Low	Low	Low	Low	Low
Kawamori (2009) (38) Japan	Low	Low	Low	Low	Low	Low
Kataoka (2012b) (39) Japan	Low	Low	Low	Low	Low	Low
Kataoka (2012) (30) Japan	Low	Low	Low	Low	Low	Low
NAVIGATOR (2010b) (40)	Low	Low	Low	Low	Low	Low
Eriksson (2006) (41) Finland	Low	Low	Low	Low	Low	Low
DeFronzo (2011) (42) US	Low	Low	Low	Low	Low	Low
DREAM (2006b) (43)	Low	Low	Low	Low	Low	Low
leRoux (2017) (44) Denmark	Low	Low	Low	Low	Low	Low
ORIGIN (2012) (45)	Low	Low	Low	Low	Low	Low
DREAM (2006) (43)	Low	Low	Low	Low	Low	Low
NAVIGATOR (2010) (40)	Low	Low	Low	Low	Low	Low
Barzilay (2011) (46)	Low	Low	Low	Low	Low	Low
Torgerson (2004) (47) Sweden	Low	Low	Low	Low	Low	Low
Tenenbaum (2005) (4) Israel	Some concerns	Some concerns	Low	Low	Low	Some concerns
Garvey (2014) (49) US	Low	Low	Low	Low	Low	Low
Kanaya (2003) (50) US	Low	Low	Low	Low	Low	Low
Dutta (2014) (51) India	Low	Some concerns	Low	Low	Low	Some concerns
Niroomand (2019) (52) Iran	Low	Low	Low	Low	Low	Low

Pittas (2019) (53) US	Low	Low	Low	Low	Low	Low
Jorde (2016) 54) Norway	Some concerns	Low	Low	Low	Low	Low
Ranasinghe (2018) (55) Srilanka	Low	Low	Low	Low	Low	Low
Honsek (2018) (56) Germany	Low	Low	Low	Low	Low	Low
Monti (2012) (57) Italy	Low	Low	Low	Low	Low	Low
Monti (2018) (58) Italy	Low	Low	Low	Low	Low	Low
Ali (2011) (59) US	Low	Low	Low	Low	Low	Low

Appendix 4a - Quality chart for Intention to treat studies

Unique ID	Study ID		Experimental	Comparator	Outcome	Weight	Randomization process	Deviations from intended interv	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall
LS1		1	SMS group	Standard of Cai	Diabetes Incide	1	+	+	+	+	+	+
LS2		2	Daily meal repl	Lifestyle educa	Diabetes Incide	1	?	+	+	−	+	!
LS3		3	Lifestyle edu +	Lifestyle edu +	Diabetes Incide	1	+	+	+	?	+	+
LS4		4	4 group sessior	4 group sessior	Diabetes Incide	1	+	?	+	+	+	+
LS5		5	Individual cour	Group counsell	Diabetes Incide	1	?	+	+	+	+	+
LS7		7	Lifestyl	Control	Diabetes Incide	1	+	−	+	?	+	!
LS9		9	Intensive dietar	Minimal dietary	Diabetes Incide	1	?	+	+	+	+	+
LS10		10	Hospitalization	Only diabetes s	Diabetes Incide	1	+	+	+	+	+	+
LS11		11	Individual diet a	Briefly informec	Diabetes Incide	1	+	?	+	+	+	+
LS12		12	Dietary and PA	No dietary or P/	Diabetes Incide	1	+	+	+	+	+	+
LS16		16	Lifestyle modifi	Placebo	Diabetes Incide	1	+	+	+	+	+	+
LS17		17	Individualised (	Oral and written	Diabetes Incide	1	+	+	+	?	+	+
LS18		18	Diet + exercise	No individual ir	Diabetes Incide	1	?	?	+	?	+	!
LS20		20	6 hour group st	standard of car	Diabetes Incide	1	+	+	+	+	+	+
LS21		21	Individual there	Group therapy (	Diabetes Incide	1	?	?	+	−	+	!
LS22		22	Screening and	Control group	Diabetes Incide	1	+	+	+	+	+	+
LS23		23	Telephone deli	Intervention thr	Diabetes Incide	1	+	+	+	+	+	+
LS24		24	Lifestyle and P.	Standard of Cai	Diabetes Incide	1	+	+	+	+	+	+
LS25		25	Intense synthet	Standard of Cai	Diabetes incide	1	+	+	+	+	+	+
LS28		28	Lifestyle peer s	Lifestyle educa	Diabetes Incide	1	+	+	+	+	+	+
LS30		30	Group based e(	Standard of car	Diabetes Incide	1	+	+	+	+	+	+
LS33		33	Metformin	placebo	Diabetes Incide	1	+	+	+	+	+	+
LS35		35	Metformin	Placebo	Diabetes Incide	1	+	+	+	+	+	+
LS36		36	Metformin	Placebo	Diabetes Incide	1	+	+	+	+	+	+
LS38		38	Metformin	Standard of car	Diabetes Incide	1	+	+	+	+	+	+
LS39		39	Acarbose	Placebo	Diabetes Incide	1	+	+	+	+	+	+
LS40		40	Acarbose	Placebo	Diabetes Incide	1	+	+	+	+	+	+
LS41		41	Voglibose	Placebo	Diabetes Incide	1	+	+	+	+	+	+
LS42		42	Voglibose	Lifestyle modifi	Diabetes Incide	1	+	+	+	+	+	+
LS43		43	Nateglinide	Lifestyle modifi	Diabetes Incide	1	+	+	+	+	+	+
LS44		44	Nateglinide	Placebo	Diabetes Incide	1	+	+	+	+	+	+
LS47		47	Rosiglitazone	Placebo	Diabetes Incide	1	+	+	+	+	+	+
LS49		49	Insulin Glargin	Placebo	Diabetes Incide	1	+	+	+	+	+	+
LS50		50	Ramipril	Placebo	Diabetes Incide	1	+	+	+	+	+	+
LS51		51	Telmisartan	Placebo	Diabetes Incide	1	+	+	+	+	+	+
LS52		52	Valsartan	Placebo	Diabetes Incide	1	+	+	+	+	+	+
LS53		53	Orlistat	Placebo	Diabetes Incide	1	+	+	+	+	+	+
LS54		54	Bezafibrate	Placebo	Diabetes Incide	1	?	?	+	+	+	!
LS55		55	PHENTPM ER	Placebo	Diabetes Incide	1	+	+	+	+	+	+
LS56		56	Hormone therap	Placebo	Diabetes Incide	1	+	+	+	+	+	+
LS58		58	Vitamin D	Placebo	Diabetes Incide	1	+	+	+	+	+	+
LS59		59	Vitamin D	Placebo	Diabetes incide	1	+	+	+	+	+	+
LS60		60	Vitamin D	Placebo	Diabetes Incide	1	?	+	+	+	+	+
LS62		62	Fibre	Placebo	Diabetes Incide	1	+	+	+	+	+	+
LS64		64	L-Arginine	Placebo	Diabetes Incide	1	+	+	+	+	+	+
LS65		65	Chromium	Placebo	Diabetes Incide	1	+	+	+	+	+	+

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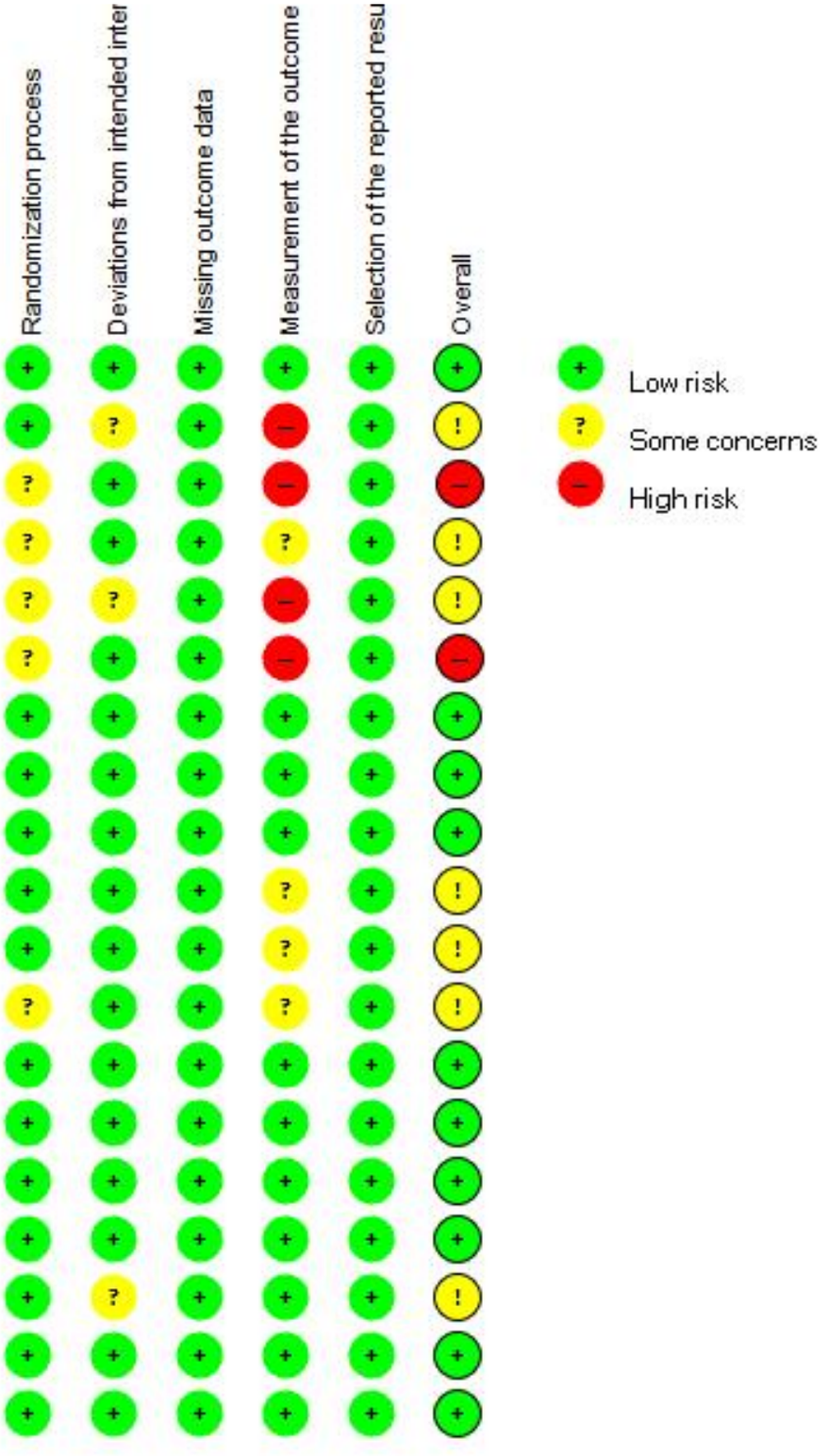
+ Low risk
? Some concerns
− High risk

Appendix 4b - Quality chart for per protocol analysis studies

Unique ID	Study ID		Experimental	Comparator	Outcome	Weight
LS6		5	Standard of Care	Standard of Care	Diabetes Incider	1
LS8		8	Bseline LS educ	Only 1 baseline L	Diabetes Incider	1
LS13		13	Lifestyle modific	Standard of care	Diabetes Incider	1
LS14		14	Repeated and de	Standard of care	Diabetes Incider	1
LS15		15	diet and PA	diet and PA for l	Diabetes Incider	1
LS19		19	Lifestyle modific	Standard health	Diabetes Incider	1
LS26		26	Short text messa	Standard of care	Diabetes Incider	1
LS27		27	Intensive lifestyl	Placebo	Diabetes Incider	1
LS29		29	Education suppo	Standard of care	Diabetes Incider	1
LS31		31	Reduced fat diet	Control diet	Diabetes Incider	1
LS32		32	Metformin	Routine care	Diabetes Incider	1
LS34		34	Metformin	Control	Diabetes Incider	1
LS37		37	Metformin	Placebo	Diabetes Incider	1
LS45		45	Glipizide	Placebo	Diabetes Incider	1
LS46		46	Pioglitazone	Placebo	Diabetes Incider	1
LS48		48	Liraglutide	Placebo	Diabetes Incider	1
LS57		57	Vitamin D + Calc	Calcium	Diabetes Incider	1
LS61		61	Zinc	Placebo	Diabetes Incider	1
LS63		63	L-arginine	Placebo	Diabetes Incider	1



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