Efficacy and Safety of Metformin for Obesity: A Systematic Review

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Abbreviations:
BMI: body mass index
US: United States
RCT: randomized controlled trial
HOMA-IR: homeostatic model assessment insulin resistance
NAFLD: non-alcoholic fatty liver disease
FPG: fasting plasma glucose
GI: gastrointestinal
CI: confidence interval
SD: standard deviation

Table of contents summary: This systematic review assesses the efficacy and safety of metformin, compared to placebo, in children and adolescents with obesity.

What's known about this subject: The worldwide prevalence of obesity has increased dramatically in the last decades among children and adolescents. Metformin is used off-label for the treatment of insulin resistance, prediabetes, and obesity in children and adolescent, however its efficacy and safety remain unclear.

What this study adds: In this systematic review, metformin therapy results in modest benefits on body mass index, weight, and insulin resistance compared with placebo. However, metformin therapy was also associated with a doubling of the rate for gastrointestinal adverse effects compared to placebo.

Contributors' statement

Dr. Masarwa developed the study question, conducted the literature search, screening, data extraction, and quality assessments, and wrote the manuscript.
Dr. Aloe contributed to the conceptualization of the study question, participated in the screening and data extraction, interpreted the data, and critically reviewed the manuscript for important intellectual content.
Ms. Brunetti conducted data extraction and quality assessment, interpreted the data, and critically reviewed the manuscript for important intellectual content.
Drs. Henderson and Platt interpreted data and critically reviewed the manuscript for important intellectual content.
Dr. Filion supervised the study, conceived the study question, interpreted data, and critically reviewed the manuscript for important intellectual content. Dr. Filion is the guarantor.
All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

ABSTRACT

Context: The efficacy and safety of metformin for obesity in children and adolescents remain unclear.

Objective: To assess the efficacy and safety of metformin via systematic review.

Data Sources: PubMed, Embase, the Cochrane Library, Scopus, and ClincalTrials.gov (inception to November 2019).

Study Selection: Randomized controlled trials (RCTs) assessing the efficacy and safety of metformin with lifestyle interventions compared to placebo with lifestyle interventions in children and adolescents with obesity.

Data Extraction: Two researchers independently extracted data and assessed quality. The primary outcomes were mean changes from baseline in body mass index (BMI), BMI z-score, homeostatic model assessment insulin resistance (HOMA-IR), and gastrointestinal adverse effects.

Results: Twenty-four RCTs (1,623 patients, range: 16 to 151) were included. Ages ranged from 4 to 19 years, and follow-up ranged from 2 months to 2 years. Metformin resulted in a modest decrease in BMI (range of mean values: −2.70 to 1.30 kg/m^2 vs −1.12 to 1.90 kg/m^2), BMI z-score (range of mean values: −0.37 to −0.03 vs −0.22 to 0.15), and HOMA-IR (range of mean values: −3.74 to 1.00 vs −1.40 to 2.66). Metformin resulted in a higher frequency of gastrointestinal adverse effects (range: 2% to 74% vs 0% to 42%).

Limitations: The available evidence is of varying quality, with high heterogeneity between trials, suggesting some uncertainty in the benefits of metformin in this population.

Conclusions: This systematic review of RCTs suggests that metformin has modest but favorable effects on weight and insulin resistance, and a tolerable safety profile among children and adolescents with obesity.

BACKGROUND

Approximately 43 million worldwide children are with overweight, and 92 million are considered to be at risk of overweight.[1] The Centers for Disease Control and Prevention defines a body mass index (BMI) >95th percentile as class-I obesity.[2] The prevalence of obesity has increased dramatically over the last decades.[3] In 2016, the prevalence of class-I obesity among children in the United States (US) was 19%.[4] Obesity is the most common cause of insulin resistance in children,[5] and it is associated with dyslipidemia, type 2 diabetes, and long-term vascular complications, among others.[6,7]

Although lifestyle interventions remain the standard of care for childhood obesity, many children will eventually require drug therapy.[8,9] Metformin is not approved for use among those aged less than 18 years in Canada. In the United States, metformin is the only approved oral medication for use in children aged >10 years with type 2 diabetes.[10,11] Several randomized controlled trials (RCTs) conducted in children demonstrated promising short-term (≤ 6 months) results regarding weight loss and Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) levels compared to placebo and lifestyle interventions.[12-14] However, other studies demonstrated no benefit.[15,16] These individual studies included small numbers of participants, had variable follow-up durations, and produced heterogeneous results. In addition, adverse effects were usually secondary endpoints.[15-19] Therefore, we conducted a systematic review to assess the efficacy and safety of metformin with lifestyle interventions, compared to placebo with lifestyle intervention, in children and adolescents with obesity, focusing on body mass index (BMI), insulin resistance, and gastrointestinal (GI) adverse effects.

METHODS

Protocol information

Our systematic review followed a pre-specified protocol, which was registered on PROSPERO (No. CRD42019126099, April 16, 2019). Results are reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (Supplementary Data).[20,21]

Search strategy

We systematically searched PubMed, Embase, the Cochrane Library, Scopus, and ClinicalTrials.gov from inception to January 2019 for RCTs and observational studies that compared metformin with or without lifestyle interventions to placebo with or without lifestyle interventions in children and adolescents (0-19 years) with obesity (with and without insulin resistance), prediabetes, or non-alcoholic fatty liver disease (NAFLD), defined by a liver biopsy with >5% steatosis within a 6 month period. We updated the search in November 2019. MeSH terms were used in PubMed and the Cochrane Library, and EMTREE terms in Embase. There were no language restrictions. The detailed search strategy is available in Supplementary Data. We manually searched bibliographies of studies to retrieve additional studies that may not have been identified in our electronic search. Investigators were contacted for unpublished data.

Study selection

The screening process and management of search results was carried out in Rayyan QCRI.[22] The titles and abstracts were screened independently by two reviewers (RM and SA), with any publication deemed potentially relevant by either reviewer carried forward for full-text evaluation. Disagreements during full-text review were resolved by consensus or, when necessary,

by a third independent reviewer (VCB). We restricted inclusion to RCTs examining metformin with lifestyle interventions compared to placebo with lifestyle interventions; lifestyle intervention represents the current standard of care for obesity in this population[2,8] We included RCTs if they reported any of the following: BMI (kg/m^2), BMI z-score, body weight (kg), fasting plasma glucose (FPG, mg/dl), HOMA-IR, waist circumference (cm), total cholesterol (mg/dl), triglycerides (mg/dl), GI adverse effects (i.e., nausea, vomiting, diarrhea, abdominal pain, loose stool), and hepatic toxicity, defined as abnormal liver function tests. Mean change from baseline in BMI, BMI z-score, and HOMA-IR, and the incidence of GI adverse effects were the primary endpoints. Although our pre-specified protocol included observational studies, given the important limitations of this literature (mainly confounding by indication), they were excluded from the final systematic review. Furthermore, we excluded studies conducted among children with type 2 diabetes given the established use of metformin for type 2 diabetes and the corresponding lack of clinical equipoise.

Data extraction

Two independent reviewers (RM and either SA or VCB) extracted data using a standardized form. For each trial, the following data were extracted: publication year, location, number of randomized patients, dose, follow-up duration, age, indication, outcomes, baseline anthropometric and metabolic measures, mean change from baseline, and adverse effects (focusing on GI adverse effects). When multiple follow-up periods and endpoints were reported for a given study, we extracted data from the publication with the most comprehensive reporting of outcomes and/or the longest follow-up.

Quality Assessment

The quality of RCTs was assessed using the Cochrane Collaboration's tool for assessing risk of bias (ROB 2).[23] The tool is structured into five domains through which bias may be introduced. The five domains are: bias arising from the randomization process, bias due to deviations from the intended interventions, bias due to missing data, bias in measurement of the outcome, and bias in selection of the reported results. We focused our quality assessment on the primary outcomes BMI and BMI z-score. Each domain was assigned a "high", "low", or "unclear" risk of bias. Two reviewers (RM, VCB) assessed quality independently, with disagreements adjudicated by a third reviewer (KBF).

Transformation methods for standardized metrics

Mean difference from baseline and standard deviation (SD) for each treatment arm were extracted for continuous outcomes. Estimation of the mean difference from baseline and SD for studies that reported continuous outcomes as mean and standard error or 95% CI, median and interquartile range, or median, minimal, and maximal value were estimated using the method described by Hozo et al.[24] Version 3.5.3 of the R Environment was used to construct forest plots to graphically present study-specific treatment effects.

RESULTS

Search results

Our systematic search is described in **Figure 1**. Our systematic search yielded 2,799 citations, of which 70 citations were considered for full-text review. Twenty-four RCTs were included in the systematic review, with 8 RCTs reporting absolute values for continuous outcomes, and 16 RCTs reporting mean changes from baseline for continuous outcomes or rates of adverse effects.

Study and patient characteristics

Study characteristics of RCTs are summarized in **Table 1** and **Supplementary Table 1**. The 24 included RCTs randomized 1,623 (range: 16 to 151) children and adolescents to metformin (861 participants) or placebo (762 participants). The indication for metformin was uncomplicated obesity in 10 RCTs, obesity with insulin resistance in 9 RCTs, prediabetes in 3 RCTs, and NAFLD in 2 RCTs. All RCTs except one[25,26] included a lifestyle co-intervention in both treatment arms. The age of participants ranged from 4 to 19 years. A total of 9 RCTs included prepubertal, pubertal, and postpubertal children and adolescents,[13,14,27-33] 10 RCTs included pubertal and postpubertal children,[12,15,19,25,26,34-38] and 5 RCTs included prepubertal and pubertal children and adolescents.[17,39-42] The duration of RCTs ranged from 2 months to 2 years. GI adverse effects included diarrhea, abdominal pain, epigastric pain, anorexia, vomiting, nausea, loose stool, and were reported in 16 RCTs overall. The total daily dose of metformin ranged from 500 to 2,000 mg/day, and 60% to 90% of children in the metformin treatment group adhered to the treatment regimen.

Quality assessment

Of the 24 included RCTs, 14 were of low to moderate quality (**Supplementary Table 2**). Nine trials had some concern of bias in the randomization process. A total of 14 RCTs had some concern for bias due to the selection of the reported outcomes. Concerns of high risk of bias were observed for deviations from the intended interventions in 11 trials and missing outcome data as a result of high rates of loss to follow-up in 6 trials. Although individual RCTs reported similar rates of loss to follow-up across treatment arms, the rates of loss to follow-up across studies ranged from 5% to 80% among subjects randomized to metformin and from 5% to 50% among those randomized to placebo.

Efficacy

The effect of metformin on our primary efficacy outcomes is reported in **Table 2**. Among the 14 RCTs that reported BMI, metformin was modestly efficacious at decreasing BMI (range of mean changes: −2.70 to 1.30 kg/m^2) compared to placebo (range of mean changes: −1.12 to 1.90 kg/m^2). The mean difference in the treatment effect between the metformin and the placebo arms ranged from −2.72 to 0.70, and the 95% CI ranged from −4.43 to 0.31. However, results across studies were heterogeneous, with 11 RCTs suggesting that metformin decreases BMI, and 3 RCTs suggesting that it increases BMI (**Figure 2)**. Furthermore, the mean change in BMI was not larger in studies that included children with higher mean BMI at baseline. Importantly, many RCTs reported variable treatment effects, preventing definitive conclusions from being drawn from individual trials. Among the 7 RCTs that reported BMI z-score, metformin consistently resulted in a decrease in BMI z-score (range of mean changes: −0.37 to −0.03) compared to placebo (range of mean changes: −0.22 to 0.15) (**Figure 3).** The mean difference in the treatment effect between

the metformin and the placebo arms ranged from −0.15 to −0.07, and the 95% CI ranged from −0.51 to 0.05 (**Figure 3**). The largest decrease in BMI z-score was observed in children and adolescents with NAFLD.[39] In addition, among 11 RCTs that examined insulin resistance, metformin resulted in modest but favorable effects on insulin resistance (range of mean changes: −3.74 to 1.00) compared to placebo (range of mean changes: −1.40 to 2.66). The mean difference in the treatment effect between the metformin and the placebo arms ranged from −3.54 to 2.03, and the 95% CI ranged from −6.80 to 8.22 (**Figure 4**). Although heterogeneity was present, metformin appeared to reduce HOMA-IR in 8 RCTs; as with BMI, some trials were inconclusive due to wide 95% CIs (**Figure 4)**.

Compared with placebo, metformin had heterogeneous effects on other efficacy endpoints. Among 7 RCTs, metformin was associated with greater weight loss (range of mean changes: −5.1 to 12 kg) compared to placebo (range of mean changes: −1.7 to 12.7 kg), resulting in overall decrease in weight in 6 RCTs (**Supplementary Figure 1**). Metformin's effects on waist circumference, FPG, total cholesterol, or triglycerides were very heterogeneous and inconclusive. (**Supplementary Figures 1 to 5)**.

Safety

Sixteen RCTs reported adverse effects during follow-up. Metformin treatment was associated with a higher report rate of adverse GI effects (rate range: 2% to 74%) compared to placebo (rate range: 0% to 42%) (**Table 3; Figure 5)**. Evidence regarding a potential increased risk of liver toxicity was inconclusive, with only 4 RCTs reporting potential liver toxicity, and heterogeneous results across studies (**Supplementary Figure 6)**. Adverse effects were not

stratified by ethnicity in the included RCTs. Seven RCTs did not report the occurrence of adverse effects, with 6 studies conducted in the US and one study in Mexico.

DISCUSSION

Our study was designed to examine the efficacy and safety of metformin with lifestyle interventions, compared to placebo with lifestyle interventions, in children and adolescents with obesity. We found that metformin has modest but favorable effects on BMI, BMI z-score, and HOMA-IR, relative to placebo. However, the available evidence is of varying quality, with high drop-out rates, and higher quality studies had smaller estimated treatment effects, suggesting some uncertainty in its clinical benefits. Metformin was also associated with almost a doubled rate of GI adverse effects compared to placebo, and the currently available evidence is inconclusive for liver toxicity.

The findings of our systematic review add to the existing literature suggesting that metformin therapy has a modest favorable effect in children and adolescents with obesity. However, the clinical significance and the long-term effects of these beneficial effects in this population remain uncertain. These findings are partially consistent with previously published systematic reviews and meta-analyses.[43-47] Although these previous knowledge syntheses examined metformin therapy for insulin resistance and obesity in children and adolescents, they had important methodological limitations. These syntheses one recent meta-analysis,[46] and several systematic reviews, and one older meta-analysis.[43-45,47] that focused on absolute BMI, did not examine BMI z-score, and did not assess safety outcomes. The meta-analyses pooled data across trials despite substantial heterogeneity in mean age across studies and substantial loss to follow-up.[45-47] Moreover, they pooled data for continuous outcomes at the end of follow-up rather than pooling the mean change from baseline, which is a more accurate estimate of the treatment effect. These previous syntheses also included studies of patients with type 2 diabetes and those of

pharmacotherapies in addition to metformin. The inclusion of such studies limits the capability to assess the efficacy and safety of metformin therapy in insulin resistance and obesity. With inclusion restricted to trials with metformin monotherapy and synthesis focused on the qualitative assessment in light of the substantial heterogeneity in the included trials, and the examination of mean changes in outcomes from baseline, our systematic review has overcome many of the limitations of the previous studies. Finally, we included BMI z-score as an endpoint, which is the preferred measure for obesity in the pediatric population.[48,49]

The observed effects of metformin on changes in BMI and weight were not consistent across trials. Absolute BMI is not the ideal measure for obesity in children and adolescents, since BMI varies with sex and age. With metformin-related weight loss superimposed on the naturally occurring weight gain associated with growth, changes in BMI translate differently among prepubertal and pubertal children and adolescents, especially when not compared across an age and sex adjusted reference.[48,49] To better assess the effects of metformin on BMI, it is crucial to examine changes in BMI z-score, a measure of relative weight for height compared to a reference standard that accounts for age and sex, rather than absolute change in BMI.[48,49] All trials that reported changes in BMI z-score showed a consistent decrease with metformin, with the largest decrease observed among individuals with NAFLD. Furthermore, improvement in absolute weight, if not adjusted to reference norms accounting for age, sex and height, may have very little clinical value when comparing children of different ages and developmental stages. Consequently, weight loss and changes in absolute BMI may not be as clinically meaningful outcomes in obese children and adolescents as in adults.[50] These issues underscore the importance of examining BMI z-score as a primary outcome in clinical trials, and other measures of adiposity such as insulin resistance, FPG, waist circumference adjusted for age, sex and height and lipid profile.

Insulin resistance measured by HOMA-IR decreased in the metformin treatment arm, indicating modest efficacy. However, these changes must be interpreted carefully, since changes in insulin resistance may be different among school aged children and adolescents due to their different stages of pubertal development and changes in other hormones.[51] The majority of trials included prepubertal and pubertal children and adolescents but did not present results stratified by age or developmental stage. The measurement of developmental stage varied, assessed by either a trained endocrinologist/nurse or reported by caregivers, further limiting the clinical interpretation of the results. Furthermore, metformin's primary mechanism of action is through lowering hepatic glucose production, with much smaller effects on insulin resistance.[10,46,52] However, a mediation analysis to quantify how much of the observed effect on insulin resistance can be attributed to weight loss versus a direct drug effect is not possible with the aggregated nature of the data. Finally, the effect of metformin on both weight loss and insulin resistance was consistent only among individuals with NAFLD; however, the trial of patients with NAFLD had longer follow-up time (2 years) than other included trials, and it is unclear if this difference is due to differences in patient populations or long-term adherence to therapy.

The number of studies that assessed changes in FPG, waist circumference, and lipid profile was small. For FPG, the studies showed an overall decrease, whereas the effects on waist circumference and lipid profile were heterogeneous and inconclusive. In most trials, mean change in waist circumference was not adjusted for age sex, and height, and therefore the results have little applicability in the clinical setting.[2] The heterogeneity in the observed treatment effects in our systematic review may also be attributed to differences in adherence, large percentages of loss to follow-up, intensity of concurrent lifestyle modifications, co-medications, and tolerance of adverse effects.

Metformin is approved for use in children and adolescents for type 2 diabetes only, and the prescribing of metformin for insulin resistance, prediabetes, and obesity remains controversial. In a study of adults aged at least 25 years with prediabetes, metformin plus lifestyle interventions, compared to lifestyle interventions and placebo, resulted in a lower cumulative incidence of type 2 diabetes after 3 years of follow-up.[53] Lifestyle interventions were more effective than metformin in people ≥60 years, less effective than metformin in adults aged 45-59 years old, and as effective in adults aged ≤44 years. These beneficial effects in adults with prediabetes and glucose intolerance are not observed in children and adolescents.[54-56] In our systematic review, 3 RCTs assessed the efficacy of metformin in children and adolescents with prediabetes.[13,14,38] These trials showed a modest decrease in BMI z-score, and no change in insulin resistance and FPG, suggesting that metformin is not as effective in the treatment of prediabetes in children and adolescents. In children and adolescent, prediabetes is often a transient condition, and the determinants of progression to over type 2 diabetes remain uncertain in this population.[54-56] Results from our study do not allow us to conclude whether metformin treatment in children and adolescents with prediabetes is beneficial or not to prevent the progression to overt type 2 diabetes.

Generally, in adults and adolescents clinically significant responses to metformin are not seen at doses less than 1,500 to 2,000 mg/day among patients with type 2 diabetes.[57] The metformin dose used in trials included in our systematic review ranged from 500 to 2,000 mg/day, and there was no clear trend regarding a potential dose-response effect on BMI, BMI z-score, and HOMA-IR. Furthermore, the rate of GI adverse effects was slightly lower with doses up to 1,000 mg/day compared to doses of 1,500 to 2,000 mg/day. However, included trials had relatively high rates of loss to follow-up (5%-80% among patients randomized to metformin), and they did not

report the specific doses of metformin at which patients had discontinued use because of GI adverse effects.

Limitations

Our study has several potential limitations. First, our study aimed to assess high-quality evidence from RCTs, and although our systematic review included 24 RCTs, many did not report changes from baseline, preventing the assessment of treatment effects of metformin for many studies. We focused on assessing the mean change and its variance from baseline. While the exclusion of trials may have reduced the precision of our range of estimates, it likely resulted in more valid treatment effect estimates. Second, substantial heterogeneity was present in the RCTs. Given this heterogeneity and the varying quality of this literature, we focused on a qualitative review and assessed the quality of the RCTs and did not perform meta-analysis. Third, for most of our secondary endpoints, there was substantial heterogeneity in observed treatment effects, and results were inconclusive for waist circumference, FPG, lipid profile, and liver toxicity. Fourth, in the studies, loss to follow-up ranged between 5% to 80% in the metformin arm and 5% to 50% in the placebo arm. Although most studies reported similar dropout rates across treatment arms, only three studies conducted dropout analyses.[14,27,34] Substantial loss to follow-up may result in biased results.[58] In addition, adherence rates to metformin varied across studies from 60% to 90%, which may also result in attenuated treatment effects and demonstrates the challenges of drug adherence among this population. Fifth, the majority of trials had a high risk of bias, which may have resulted in some bias in estimated treatment effects. Sixth, there was substantial heterogeneity in lifestyle interventions across the studies, which may have resulted in different treatment effects of metformin, depending on the nature of the implemented diet and exercise regime. Seventh, we

were unable to assess treatment effects of metformin across different age groups and developmental stages, which may have been beneficial for the clinical interpretation of results. However, the treatment effects in trials that included only school aged children or adolescents were fairly consistent for the primary outcomes. Eighth, although a mediation analysis may have been useful, we were unable to quantify how much of the observed effect on insulin resistance can be attributed to weight loss versus a direct drug effect with the aggregated nature of the data. Finally, our study was restricted to the use of metformin monotherapy; therefore, the generalizability of our findings to its use in combination with other therapies is unknown.

CONCLUSIONS

There is some evidence that metformin therapy plus lifestyle interventions has a modest favorable effect on BMI z-score and insulin resistance, and a tolerable safety profile in children and adolescents with obesity. However, the available evidence is of varying quality, and results from higher quality studies demonstrated smaller treatment effects, suggesting some uncertainty in its benefits. Nonetheless, metformin may be considered for use as a pharmacological therapy in this pediatric population due to its modest efficacy, availability, cost, and safety profile. Future RCTs with standardized lifestyle interventions and real-world studies are required to characterize pediatric patients that may benefit most from metformin monotherapy and in combination with other drugs for the treatment of insulin resistance and obesity.

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FIGURE LEGENDS

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analysis flow diagram describing study selection process for a systematic review of trials assessing the efficacy and safety of metformin among children and adolescents with obesity.

Figure 2. Mean differences and confidence intervals from fourteen randomized controlled trials comparing change in body mass index between metformin treatment and placebo among children and adolescents with obesity.

Figure 3. Mean differences and confidence intervals from seven randomized controlled trials comparing change in body mass index z-score between metformin treatment and placebo among children and adolescents with obesity.

Figure 4. Mean differences and confidence intervals from eleven randomized controlled trials comparing mean change in homeostatic assessment model insulin resistance between metformin treatment and placebo among children and adolescents with obesity.

Figure 5. Risk ratios and confidence intervals from sixteen randomized controlled trials comparing risk for gastrointestinal adverse effects between metformin treatment and placebo among children and adolescents with obesity.

Table 1. Characteristics of randomized controlled trials examining metformin in children and youth.

Study, year	Study Design	Location	Treatment arms (No. patients randomized)	Control arm (No. patients randomized)	Indication for metformin Age	Follow-Up (Months)	Endpoints Side Effects
Warnakulasuriya et al., 2018 [41]	Triple blind RCT	Sri Lanka	Metformin 500-1,000mg BID +Structured diet + physical activity (68)	Placebo+ Structured diet+ physical activity (82)	Uncomplicated obesity 8-16 years Prepubertal+ Pubertal	12	BMI, weight, WC, FPG, HOMA-IR, Total cholesterol, TG, GI side effects, AST, ALT
Garibay Nieto et al., 2017 [29]	Double blind RCT	Mexico	Metformin 1g/day + lifestyle intervention (14)	Placebo + lifestyle intervention (17)	Uncomplicated obesity 8-18 years Prepubertal+ Pubertal+ postpubertal	4	BMI, weight, WC, HOMA-IR, TG
Pastor Villaescusa et al., 2017 [40]	Double blind RCT	Spain	Metformin 500mg BID + diet (68)	Placebo + diet (72)	Uncomplicated obesity 7-14 years Prepubertal+ Pubertal	6	BMI, weight, FPG, HOMA-IR, Tot. cholesterol, TG GI side effects
Van Der Aa et al., 2016 [33]	Double blind RCT	Netherlands	Metformin 2,000mg day + dietary diary (23)	Placebo + dietary diary (19)	Obesity with insulin resistance 10-16 years Prepubertal+ pubertal + postpubertal	18	BMI, weight, HOMA-IR, Hb1Ac GI side effects Liver toxicity
Clarson et al., 2014 [27]	RCT	Canada	Metformin extended release 500-2,000 mg OD + lifestyle changes (50)	Placebo OD + life style changes (59)	Uncomplicated obesity 10-16 years Prepubertal+ pubertal + postpubertal	12	BMI GI side effects Liver toxicity
Evia-Viscarra et al., 2012 [12]	Double blind RCT	Mexico	Metformin 500mg BID (14)	Placebo (12)	Uncomplicated obesity 9-18 years	3	BMI, weight, WC, FPG GI side effects Liver toxicity

					Pubertal + postpubertal		
Gomez-Diaz et al., 2012 [13]	Double blind RCT	Mexico	Metformin 850mg BID+ diet+ exercise (28)	Placebo+ diet+ exercise (24)	Prediabetes 4-17 years Prepubertal+ Pubertal+ postpubertal	3	BMI, weight, WC, HOMA-IR, Hb1Ac GI side effects AST ALT
Kendall D. et al., 2012 [14]	Double blind RCT	UK	Metformin 1,000 mg and 500mg OD + diet and exercise counselling (74)	Placebo + diet and exercise counselling (77)	Prediabetes 8-18 years Prepubertal+ Pubertal+ postpubertal	6	BMI, weight, FPG, HOMA-IR, Tot. cholesterol, TG GI side effects
Mauras et al., 2012 [30]	RCT ITT	USA	Metformin 500-1,000mg BID + lifestyle intervention (35)	Placebo+ lifestyle intervention (31)	Uncomplicated obesity 7-18 years Prepubertal+ pubertal+ postpubertal	6	BMI, weight, WC, HOMA-IR
Lavine et al., 2011 [39]	Double blind double dummy RCT	USA	Metformin 500mg BID + diet and exercise counselling (57)	Placebo + diet and exercise counselling (58)	NAFLD 8-17 years Prepubertal+ pubertal+	24	BMI, weight, WC, FPG, HOMA-IR, Tot. cholesterol, TG Liver toxicity ALT AST
Rynders et al., 2011 [19]	Randomized controlled trial	USA	Metformin 500mg-1,000mg BID + diet + exercise (7)	**No placebo** - diet + exercise (9)	Uncomplicated obesity 10-17 years Pubertal+ postpubertal	6	BMI, weight
Yanovski et al., 2011 [42]	Double blind RCT	USA	Metformin 1,000mg BID + diet (53)	Placebo + diet (47)	Obesity with Insulin resistance 6-12 years Prepubertal+ pubertal+	6	BMI, weight, WC, FPG, HOMA-IR, Tot. cholesterol, TG GI side effects AST ALT B12

Rezvanian et al., 2010 [31]	Triple masked RCT	Iran	Metformin-1,500mg/day + diet + exercise (41)	Placebo + diet + exercise (42)	Uncomplicated obesity 10-18 years Prepubertal+ Pubertal+ postpubertal	6	BMI , WC GI side effects
Wiegand et al., 2010	RCT	Germany and Switzerland	Metformin 500mg BID + diet (36)	Placebo + diet (34)	Prediabetes 14-16 years Pubertal+ postpubertal	6	Weight, FPG, HOMA-IR, Tot. cholesterol, TG GI side effects
Glaser Pediatric Research Network Obesity Study Group, 2010 [34]	Double-blind RCT	USA	Metformin XR 2,000mg OD + lifestyle intervention (39)	Placebo + lifestyle intervention (38)	Uncomplicated obesity 13-18 years Pubertal+ postpubertal	12	BMI, HOMA-IR, Tot. cholesterol, TG GI side effects
Clarson et al., 2009 [28]	RCT	Canada	Metformin 1,500mg OD+ life style intervention (14)	Lifestyle intervention alone (11)	Obesity with Insulin resistance 10-16 years Prepubertal+ pubertal + postpubertal	6	BMI, FPG, TG
Nadeau et al., 2009 [37]	Double blind RCT	USA	Metformin 850mg BID + wellness education (37)	Placebo+ wellness education (13)	NAFLD 12-18 years Pubertal+ postpubertal	6	BMI, weight, FPG, Tot. cholesterol, TG GI side effects AST ALT
Atabek et al., 2008 [17]	Double blind RCT	Turkey	Metformin 500mg BID + diet + exercise (90)	Placebo 500mg BID + diet + exercise (30)	Obesity with Insulin resistance 8-16 years Prepubertal+ pubertal +	6	BMI, weight, HOMA-IR, Tot. cholesterol, TG GI side effects
Burgert et al., 2008 [15]	Double blind RCT	USA	Metformin 1,500mg/day+ life style counselling (15)	Placebo+ life style counselling (17)	Obesity with Insulin resistance 13-18 years Pubertal+ postpubertal	4	BMI, weight, FPG, HOMA-IR, Tot. cholesterol, TG
Love Osborne et al., 2008 [36]	Double blind RCT	USA	Metformin 850mg BID + diet + exercise (48)	Placebo + diet + exercise (16)	Obesity with Insulin resistance 12-19 years	6	BMI GI side effects

					Pubertal+ postpubertal		
Freemark et al., 2007[25]	Double blind RCT	USA	Metformin 500mg BID (14)	Placebo (15)	Obesity with Insulin resistance 12-19 years Pubertal+ postpubertal	6	GI side effects AST ALT
Srinivasan et al., 2006 [32]	RCT	Australia	Metformin 1,000mg BID (10)	Placebo (12)	Obesity with Insulin resistance 9-18 years Prepubertal+ pubertal + postpubertal	6	GI side effects
Kay et al., 2001[35]	Double blind RCT	USA	Metformin 850mg BID+ low calorie diet (12)	Placebo+ low calorie diet (12)	Obesity uncomplicated 14-16 years Pubertal+ postpubertal	2	Weight, FPG, Tot. cholesterol, TG GI side effects
Freemark et al., 2000 [26]	Double blind RCT	USA	Metformin 500mg BID (14)	Placebo (15)	Obesity with Insulin resistance 12-19 years Pubertal+ postpubertal	6	BMI, FPG, HOMA-IR, Hb1Ac, Tot. cholesterol, TG GI side effects

Abbreviations: RCT: randomized controlled trial; BID: twice daily; BMI: body mass index; SDS: standard deviation score; SD: standard deviation; WC: waist circumference; FPG: fasting plasma glucose; HOMA-IR: homeostatic model assessment-insulin resistance; Tot: total; TG: triglycerides; GI: gastrointestinal; ALT: alanine transaminase; AST: aspartate transaminase; HbA1c: hemoglobin-A1c; OD: once daily; XR: extended release; NAFDL: non-Alcoholic Fatty liver disease.

Table 2. Obesity measures and insulin resistance at maximum follow-up in randomized controlled trials examining metformin in children and youth.

		BMI		BMI z-score		HOMA-IR	
Study, year	Follow-Up (Months)	Baseline	Mean Change	Baseline	Mean Change	Baseline	Mean Change
Warnakulasuriya et al., 2018 [41]	12						
Metformin (n=68)		27.44±2.96	−0.85±1.56	2.54±0.59	−0.37±0.29	2.63±1.21	−1.77± 3.35
Placebo (n=82)		27.44±2.7	−0.05±1.55	2.51±0.42	−0.22±0.30	2.34±1.46	−0.79±3.49
Van Der Aa et al., 2016 [33]	18						
Metformin (n=23)		29.8±4.74	−0.35±2.74	3.10±0.59	−0.12±0.42	4.00±3.00	−0.65±3.33
Placebo (n=19)		30.5±7.33	0.82±2.00	3.38±0.81	0.04±0.12	4.85±2.50	−0.07±2.14
Evia-Viscarra et al., 2012 [12]	5						
Metformin (n=14)		33.44±5.82	−0.73±0.98	NA	NA	7.84±3.66	−0.88±4.23
Placebo (n=12)		32.82±6.37	−0.72±0.85	NA	NA	5.52±3.35	2.66±4.22
Gomez-Diaz et al., 2012 [13]	3						
Metformin (n=28)		31.10±6.30	NA	NA	NA	7.50±22.00	−0.67±0.97
Placebo (n=24)		27.10±5.90	NA	NA	NA	6.50±13.18	0.12±0.26
Mauras et al., 2012 [30]	6						
Metformin		32.00±1.00	−2.40±2.95	NA	NA	4.80±0.40	0.34±4.49

(n=35)							
Placebo (n=31)		33.20±0.70	−1.12±2.78	NA	NA	5.20±0.60	1.6±4.45
Lavine et al., 2011 [39]	24						
Metformin (n=57)		34.00±5.00	1.30±2.69	2.35±0.30	−0.25±0.32	7.90±5.40	−0.50±8.85
Placebo (n=58)		33.00±6.00	1.90±3.10	2.35±0.26	0.15±0.27	11.00±17.60	−1.40±27.00
Rynders et al., 2011 [19]	6						
Metformin (n=7)		33.60±7.2	−2.70±2.38	NA	NA	5.30±1.60	NA
Placebo (n=6)		33.60±3.40	−1.00±1.01	NA	NA	4.90±3.20	NA
Yanovski et al., 2011 [42]	6						
Metformin (n=53)		34.20±6.80	−0.78±2.84	2.56±0.27	−0.11±0.20	4.50±2.20	NA
Placebo (n=47)		34.60±6.20	−1.09±3.00	2.58±0.24	−0.04±0.21	4.90±3.30	NA
Rezvanian et al., 2010 [31]	6						
Metformin (n=45)		26.40±3.35	0.9±0.1	2.40±0.06	NA	NA	NA
Placebo (n=45)		26.20±4.20	0.2±0.04	2.40±0.13	NA	NA	NA
Wiegand et al., 2010	6						
Metformin (n=34)		33.06±4.64	0.69±3.69	2.72±0.49	−0.03±0.02	4.90±1.54	NA
Placebo		32.93±6.56	0.07±0.51	2.79±0.60	−0.02±0.07	4.58±3.00	NA

(n=29)							
GPRNOS, 2010 [34]	12						
Metformin (n=39)		35.90±5.70	−0.9±3.12	2.28±0.31	−0.09±0.25	3.80±2.80	−0.10±4.99
Placebo (n=38)		35.90±4.70	0.2±3.08	2.31±0.21	−0.04±0.24	5.00±3.50	−0.80±4.31
Clarson et al., 2009 [28]	6						
Metformin (n=14)		36.40±6.73	−1.80±2.99	2.41±0.22	−0.16±0.26	5.23±1.94	−0.53±3.58
Placebo (n=11)		33.90±3.64	0.50±099	2.34±0.19	−0.02±0.09	6.54±1.92	−0.50±4.07
Atabek et al., 2008 [17]	6						
Metformin (n=90)		28.50±3.40	−2.08±5.56	NA	NA	4.95±3.34	−3.74±3.80
Placebo (n=30)		28.00±3.40	0.65±3.49	NA	NA	3.98±1.81	−1.05±2.30
Burgert et al., 2008 [15]	4						
Metformin (n=15)		41.00±6.00	−0.90±4.30	NA	NA	8.80±2.10	1.00±1.00
Placebo (n=17)		40.00±6.00	1.10±4.68	NA	NA	6.20±3.00	1.20±1.21
Love Osborne et al., 2008 [36]	6						
Metformin (n=48)		39.40±6.50	−0.16±1.89	4.60±1.80	NA	NA	NA
Placebo (n=16)		39.30±7.20	0.63±1.29	6.20±8.90	NA	NA	NA

Abbreviations: BMI: body mass index, BMI z-score: body mass index z-Score, HOMA-IR: homeostatic model assessment insulin resistance, NA: not available
*Numbers are presented as mean and standard deviation.

Table 3. Gastrointestinal adverse effects reported during follow-up in randomized controlled trials examinin youth.

Study, Year	Follow-Up (Months)	Daily Dose (mg)	GI Adverse Effects Reported	Me cas
Warnakulasuriya et al., 2018 [41]	12	1,000 to 2,000	Gastrointestinal and anorexia	25
Pastor Villaescusa et al., 2017 [40]	6	1,000	Diarrhea	9/
Van Der Aa et al., 2016 [33]	18	2,000	Nausea and diarrhea	17
Clarson et al., 2014 [27]	12	500-2,000	Diarrhea	1
Evia-Viscarra et al., 2012 [12]	5	1,000	Epigastric pain	2/
Gomez-Diaz et al., 2012 [13]	3	1,700	Diarrhea	10
Kendall D. et al., 2012 [14]	6	500 or 1,000	Diarrhea, nausea, abdominal pain	20
Yanovski et al., 2011 [42]	6	2,000	Loose stool, vomiting	21
Rezvanian et al., 2010 [31]	6	1,500	Abdominal pain, loose stool	3
Wiegand et al., 2010	6	1,000	Gastrointestinal	5/
GPRNOS, 2010 [34]	12	2,000	Nausea, vomiting	9/
Nadeau et al., 2009 [37]	6	1,700	Nausea, diarrhea, abdominal pain	10
Atabek et al., 2008 [17]	6	1,000	Vomiting	2
Love Osborne et al., 2008 [36]	6	1,700	Gastrointestinal	14
Srinivasan et al., 2006 [32]	6	2,000	Nausea	2/
Kay et al., 2001[35]	2	1,700	Nausea, loose stool	5/

Abbreviations: GI: gastrointestinal

Efficacy and Safety of Metformin for Obesity: A Systematic Review

Supplementary Data

APPENDIX A PRISMA 2009

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3-4, 7
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5-6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	7
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7-8
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix D
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8-9
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7-9

Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	10-11
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	10-11

APPENDIX B Search strategies for systematic literature search by database

Keywords:

Mesh terms: “Child”, “Adolescent”, “Biguanides”, “diabetes Mellitus, Type 2”, “Diabetes Mellitus”, “Obesity”, “Pediatric Obesity”, “Insulin resistance”, “Metabolic Syndrome”, “Body Mass Index”, “Prediabetic State”, “C-Reactive Protein”, “Waist Circumference”,

1. **PubMed**

Search	Query	Items found
#30	Search (#29 AND #27) Sort by: Author	578
#29	Search (#8 OR #9 OR #10 OR #25)	572,973
#28	Search (#8 OR #9 OR #10)	339,373
#27	Search (#5 AND #26)	2,366
#26	Search (#23 OR #24)	2,845,957
#25	Search "Body Weight"[Mesh]	432,372
#24	Search "Adolescent" [Mesh]	1,907,930
#23	Search "Child" [Mesh]	1,806,417
#10	Search "diabetes mellitus, type 2" [Mesh]	119,690
#9	Search "insulin resistance" [Mesh]	75,550
#8	Search "obesity" [Mesh]	192,906
#5	Search (#2 OR #3 OR #4)	24,506
#4	Search "Biguanides" [Mesh]	24,482
#3	Search Glucophage*	108
#2	Search "Metformin" [Mesh]	11,697

November 2019 Update

Search	Query	Items found
#19	date restriction	14
#18	Search (#17 AND #15)	681
#17	Search (#6 OR #7 OR #9 OR #13)	597,582
#16	Search (#6 OR #7 OR #9)	358,504
#15	Search (#5 AND #14)	2,467
#14	Search (#10 OR #11)	2,936,432
#13	Search "Body Weight" [Mesh]	448,712
#12	Search 'Body Weight" [Mesh]	674,770
#11	Search "Adolescent" [Mesh]	1,970,463
#10	Search "Child" [Mesh]	1,861,053
#9	Search "diabetes mellitus,type 2" [Mesh]	126,741
#8	Search "diabetes melitus,type2" [Mesh]	0
#7	Search "insulin resistance" [Mesh]	79,518
#6	Search "Obesity" [Mesh]	203,470
#5	Search ((#2) OR #3) OR #4	25,807
#4	Search "Biguanides" [Mesh]	25,779
#3	Search Glucophage*	113
#2	Search "Metformin"[Mesh]	12,619

2. EMBASE:

Search Strategy:

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1 Metformin/ (12652)

2 Obesity/ and Pediatric Obesity/ (468)

3 Insulin Resistance/ (54907)

4 Diabetes Mellitus/ (114425)

5 Child/ (1645315)

6 Body Weight/ (186359)

7 Adolescent/ (1971587)

8 (#7 or #5).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (4399494)

9 (#8 and #1).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol

supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (2077285)

10 (#2 or #4 or #3).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (8409501)

11 (#10 and #1 and #8).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (476862)

12 (child and metformin and (obesity or diabetesOR insulin resistance)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (201)

EMtree terms: “Child”, “adolescent”, “adolescent obesity”, “metformin”, “diabetes mellitus”, “childhood obesity”, “obesity”, “body mass”, “impaired glucose tolerance”, “homeostasis model assessment”

January 2019: 1140

November 2019: 5

3. Scopus (845):

(((((children) AND (adolescents)) AND (metformin OR glucophage) AND (obesity)) AND ((diabetes AND mellitus AND type 2) AND (insulin AND resistance)) AND (metabolic AND syndrome)) AND (weight)) AND (bmi)

January 2019: 845

November 2019: 54

4. Cochrane Central (42)

Search Name: metformin in Title Abstract Keyword AND children OR adolescents OR pediatrics in Title Abstract Keyword AND insulin resistance in Title Abstract Keyword AND obesity in Title Abstract Keyword AND diabetes type 2 in Title Abstract Keyword (Word variations have been searched)

Last Saved: 23/01/2019 16:01:47

Cochrane terms for children: Child*, adolesc*, Juvenil*, Pediatri*, School*, teen* or young* or youth*

ID Search

#1 metformin:ti,ab,kw AND children OR adolescents OR pediatrics:ti,ab,kw AND insulin resistance:ti,ab,kw AND obesity:ti,ab,kw AND diabetes type 2:ti,ab,kw (Word variations have been searched)

January 2019: 42

November 2019: 10

5. Clinicaltrials.gov (103)

CHILDREN OR ADOLESCENTS | DIABETES OR OBESITY OR METABOLIC SYNDROME | Metformin | Child

Also searched for Metabolism, Glucophage, Obese and more. See Search Details

Applied Filters: Child (birth–17).

January 2019: 103

November 2019: 8

APPENDIX C SUPPLEMENTARY TABLES

Supplementary Table 1. Additional characteristics of RCTs

Study, Year	Inclusion Criteria	Exclusion Criteria	Lifestyle Intervention Details	Adherence %
Warnakulasuriya et al., 2018	Obese (BMI/Age-SDS +2SD, WHO 2007)22 8- to 16year-old	Children of non-Sri Lankan origin, planning to migrate within a year, or having a secondary cause for obesity	Trained nutritionist, daily physical activity routine of 20–30 minutes was given to each child, weekly physical activity sessions of 1-hour. Physical activity diary	NA
Garibay Nieto et al., 2017	Obese BMI ≥ 95th percentile without previous intervention	BMI≥ 35 kg/m^2, endocrine or genetic obesity, diabetes, prediabetes, systemic illness, use of weight loss medications	Monthly structured physical activity session, psychoeducational group session, diet (WHO guidelines), recommendation for 60 minutes physical activity, 5 days a week	80%
Pastor Villaescusa et al., 2017	Obese BMI ≥ 95th percentile, no underlying disease, no medication for weight loss in the last 12 months, no participation in previous trial	Use of medications with metabolic effects (BBs, diuretics, steroids), monogenic obesity, children subjected to long periods of rest, no informed consent	One on one session of standardized healthy life style advice (session at beginning of trial)	89%
Van Der Aa et al., 2016	10-16 years, BMI-SDS > 2.3, HOMA-IR > 3.4, Caucasian descent, informed consent	T2DM, PCOS, corticosteroids, alcohol abuse, impaired renal function, syndromal disorder, impaired hepatic function	Physical training offered twice weekly	M-74% P-69%
Clarson et al., 2014	10-16 years, live within 30km, BMI ≥ 95th percentile for age, no contraindications for metformin or exercise	FPG > 6 mmol/L (110 mg/dl), Hb1Ac > 6%	Changing exercise intervention during trial: 1 hour, 3 times a week, 1 hour, 1 times 1 week, 1 hour, 1 time a week	75-85%

		Inability to engage in group activity, non adherent patients (<70%)		
Evia-Viscarra et al., 2012	Attend obesity clinic, Tanner stage ≥ 2	Glucose intolerance, type-1 diabetes, T2DM, anemia, creatinine ≥ 106, hepatic dysfunction, history of lactic acidosis	Instructions for lifestyle and diet modification	M-94% P-99%
Gomez Diaz et al., 2012	Medical insurance, glucose intolerance, no inflammatory disease in previous 3 months	No medical insurance, diabetes, previous diabetes, renal or hepatic disease, smoking, steroids, Primary dyslipidemia, heart conditions, metabolic acidosis , antihypertensives, lipid lowering agents, diabetes agents	Individual lifestyle program	NA
Kendall D. et al., 2012	BMI > 98th percentiles, impaired glucose tolerance or hyperinsulinemia	Glycosuria, ketonuria, chronic illness, chromosomal abnormality, renal and hepatic insufficiency, chronic diarrhea, previous lactic acidosis	Instructions for lifestyle and diet modification	NA
Mauras et al., 2012	BMI > 95th percentile, normal BP, glucose tolerance and lipid profile, CRP, Fibrinogen > 2SD above mean	Alcohol use, chronic illness, chronic medications	Dietician counseling, free gym membership, recommendation for 30 minutes workout, 3 times a week	NA
Lavine et al., 2011	NAFLD	Diabetes mellitus, cirrhosis, alcohol use, pregnancy, viral hepatitis, genetic metabolic disease	NA	NA

Rynders et al., 2011	Taner stages 4 and 5, BMI > 95th percentile, no metabolic syndrome complications, normal FPG (<100mg/dl)	Endocrine/genetic obesity, chronic medications, smoking	Structured lifestyle modification	NA
Yanovski et al., 2011	BMI > 95th percentile (CDC), prepubertal/ early pubertal, fasting hyperinsulinemia	Impaired FPG, diabetes, chronic disease , kidney or hepatic dysfunction	Monthly dietician, food diary, exercise prescription – 30 minutes	M- 93% P- 92%
Rezvanian et al., 2010	Failure on 3 month diet and exercise program, BMI > 95th percentile (CDC)	Chronic disease, endocrine/genetic obesity, MAO-Is, kidney and liver dysfunction	Advice for moderate intensity exercise every day, advice from dietician	NA
Wiegand et al., 2010	BMI > 97th percentile, signs of MS, impaired FPG, HOMA-IR > 3	Pre existing diabetes, pregnancy, elevated (>1.5 UL) liver enzymes, creatinine > 1.5mg/dl, chronic mental illness	Multi-professional diet and exercise sessions	<70%
GPRNOS Group, 2010	BMI > 95th percentile, weight <136 kg	Previous DM diagnosis, previous use of DM medication, anti obesity medication, recent steroid therapy, weight loss program last 6 monts, genetic endocrine obesity, elevated creatinine and liver enzymes, alcohol use, pregnancy , impaired mobility	10 individualized once weekly diet and exercise sessions	NA
Clarson et al., 2009	Obese, insulin resistance	NA	NA	NA

Nadeau et al., 2009	Obesity, BMI > 30 kg/m2 or 95th percentile, fasting insulin >25, HOMA-IR > 3.5	Pre-existing diabetes, pregnancy, creatinine > 1.5, heart disease, liver disease, Hepatitis B, C	Standardized video about healthy eating habits , participants choose diet of exercise goals (3)	NA
Atabek et al., 2008	Hyperinsulinemia , BMI > 95th percentile	Major illness, type-1 diabetes, T2DM, chronic medications, Cushing's syndrome, family history of DM	Individually tailored diet and exercise (at least 30 minutes, 4 days a week)	NA
Burgret et al., 2008	Tanner 3-5, healthy, insulin > 30, normal FPG (<100)	Smoking, hepatic disease, liver functionsX2 UNB, chronic medications	Nutritional and exercise recommendations	M- 94% P-91%
Love Osborne et al., 2008	Insulin > 25, HOMA-IR > 3.5, BMI > 95th percentile, family history T2DM, Acanthosis Nigricans	Pre-existing diabetes, pregnancy , liver functions X 1.5 UNB, creatinine > 1.5	Diet consulting and exercise	M- 60% P- 75%
Freemark et al., 2007	Tanner ≥ 3, BMI> 30 kg/m2, insulin > 15, first or second degree relative with T2DM, FPG < 100, Hb1Ac < 6	Chronic medications, renal disease, liver disease, alcohol use	No dietary restrictions	NA
Srinivasan et al., 2006	Insulin resistance , Acanthosis Nigricans, HOMA-IR > 3.5	Type 1 diabetes, T2DM, CI to metformin, MRI, weight > 120kg	None	M- 78% P- 78%
Kay et al., 2001	BMI > 30 kg/m2	Glucose intolerance, diabetes, endocrine disease, FPG > 120, Hb1Ac > 7.5	Hypocaloric diet plus placebo for 1 week before randomization – to exclude non compliant patients, diet instruction	M- 81% P-85%

Freemark et al., 2000	Tanner ≥ 3, BMI> 30 kg/m2, insulin > 15, first or second degree relative with T2DM, FPG < 100, Hb1Ac < 6	Chronic medications, renal disease, liver disease, alcohol use	No dietary restrictions	NA
Abbreviations: BMI: body mass index; SDS: standard deviation score; FPG: fasting plasma glucose; HOMA-IR: homeostatic model assessment-insulin resistance; Tot: total; ALT: alanine transaminase; AST: aspartate transaminase; HbA1c: hemoglobin-A1c; NAFDL: non-Alcoholic Fatty liver disease; M: metformin; P: placebo.				

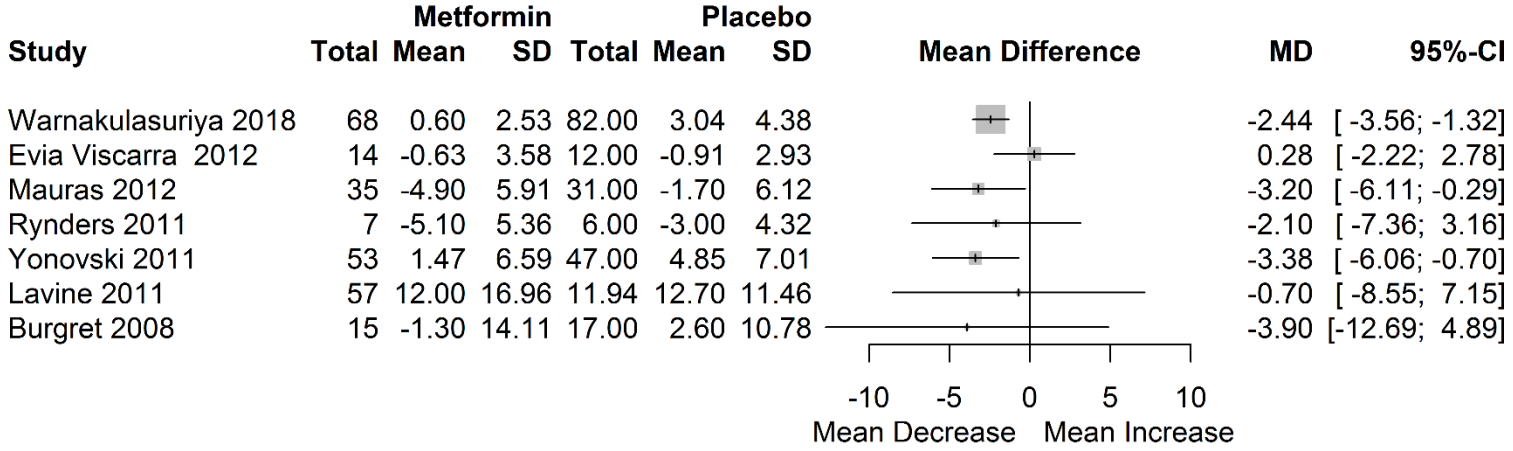
Supplementary Table 2. ROB-2 Quality Assessments for RCTs comparing metformin with lifestyle intervention versus placebo with lifestyle intervention for the treatment of insulin resistance and obesity in children.

Study ID	Outcome	Aim	Weight	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall Bias
Warnakulasuriya	BMI	PP	1	Low	Some concerns	High	Low	Low	Some concerns
Pastor Villaescusa	BMI	PP	1	Low	Low	Low	Low	Low	Low
Van Der aa	BMI	PP	1	Low	Low	High	Low	Low	High
Clarson et	BMI	ITT	1	Low	Low	Low	Low	Low	Some concerns
Evia Viscara	BMI	PP	1	Some concerns	Some concerns	Low	Low	Some concerns	Some concerns
Gomez Diaz	BMI	PP	1	Low	High	Low	Some concerns	Some concerns	High
Kendall D.	BMI	PP	1	Low	Some concerns	Low	Low	Some concerns	Some concerns
Mauras	BMI	ITT	1	High	High	Some concerns	Some concerns	High	High
Lavine	Liver enzymes	ITT	1	Low	Low	Low	Some concerns	Low	Low
Rynders	BMI	PP	1	High	High	High	Low	Some concerns	High
Yanovski	BMI	ITT	1	Low	Low	Low	Low	Some concerns	Some concerns

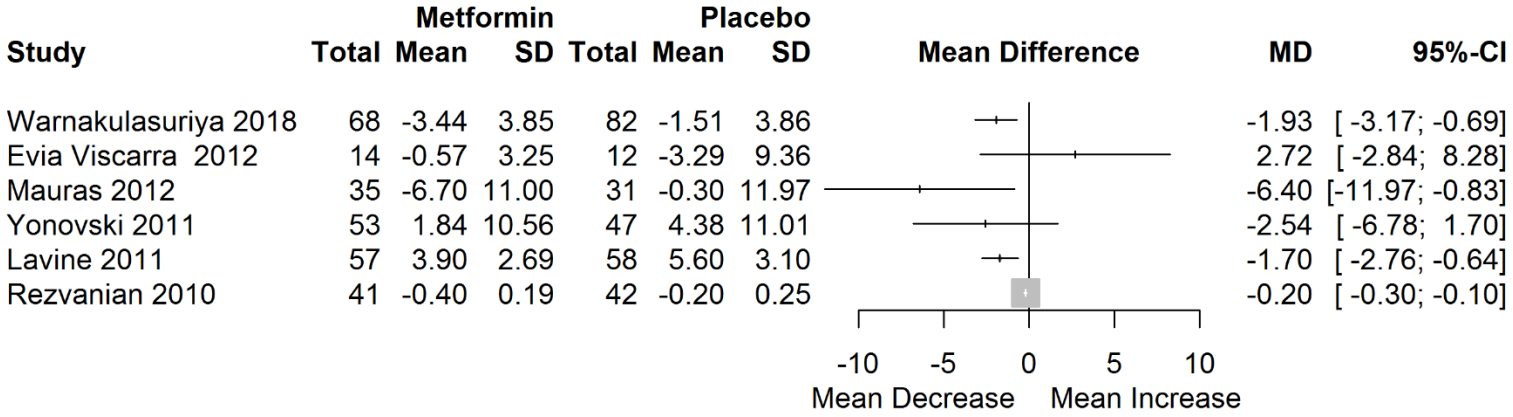
Rezvanian	BMI	PP	1	Low	Some concerns	Low	Low	Some concerns	Some concerns
Wiegand	BMI	ITT	1	Low	High	Low	Low	Some concerns	High
GPRNOS	BMI	ITT	1	Low	Some concerns	Some concerns	Low	Low	Some concerns
Clarson	BMI	PP	1	Some concerns	High	Low	Low	Some concerns	High
Nadeau	BMI	ITT	1	High	Low	Low	Low	Low	Some concerns
Atabek	BMI	ITT	1	Some concerns	High	Low	High	Some concerns	High
Burgert	BMI	PP	1	Low	Low	Low	Low	Some concerns	Some concerns
Love Osborne	BMI	PP	1	High	High	Low	Low	Some concerns	High
Freemark	Liver enzymes	PP	1	Some concerns	Some concerns	Low	Low	Some concerns	High
Freemark	BMI	ITT	1	Some concerns	High	High	Low	Some concerns	High
Srinivasan	BMI	PP	1	Some concerns	High	Some concerns	Some concerns	High	High
Kay	Weight	ITT	1	Some concerns	High	Low	Some concerns	Low	High
Garibay Nieto	BMI	PP	1	Some concerns	Low	High	Low	Low	High

Abbreviations: BMI: body mass index PP: per-protocol analysis- only completed the treatment originally allocated are include din the analysis , ITT: intention-to-treat analysis- all randomized patients are included in the analysis

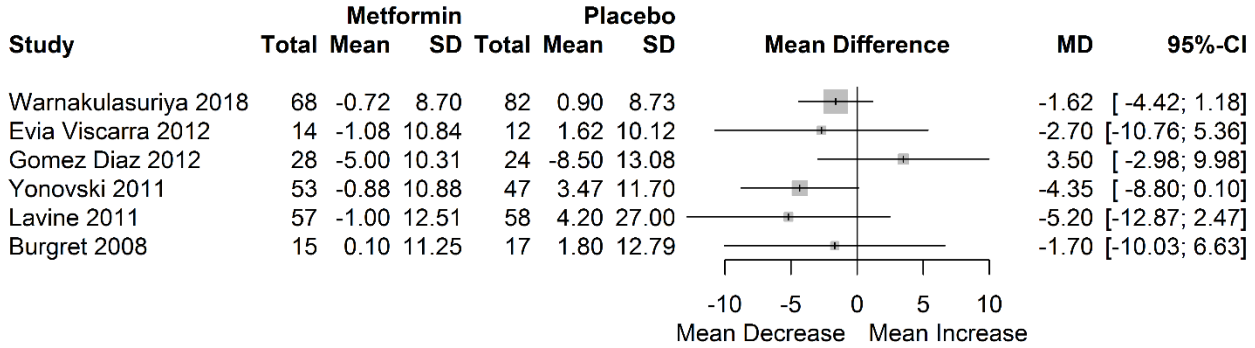
Supplementary Figure 1. Mean differences, and confidence intervals, from 7 randomized controlled trials comparing mean change in weight between metformin treatment and placebo.



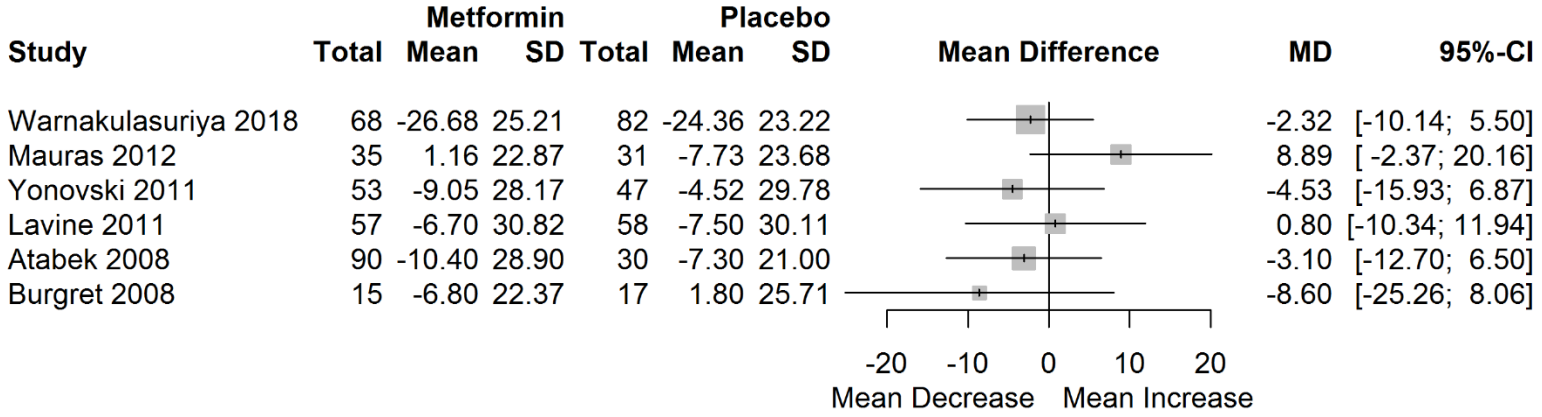
Supplementary Figure 2. Mean differences, and confidence intervals, from 7 randomized controlled trials comparing mean change in waist circumference between metformin treatment and placebo.



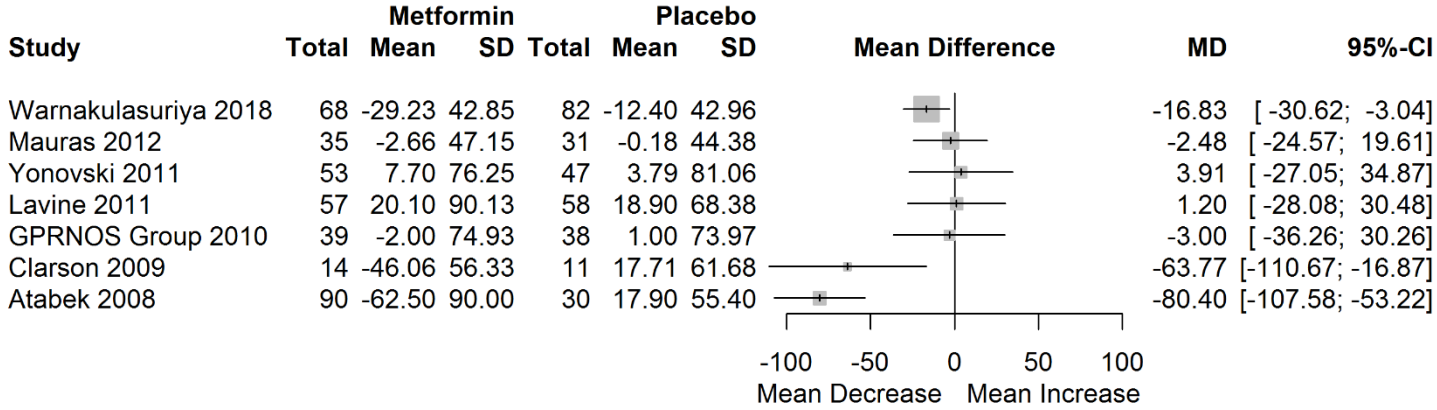
Supplementary Figure 3. Mean differences, and confidence intervals, from 6 randomized controlled trials comparing mean change in fasting plasma glucose between metformin treatment and placebo.



Supplementary Figure 4. Mean differences, and confidence intervals, from 6 randomized controlled trials comparing mean change in total cholesterol between metformin treatment and placebo.



Supplementary Figure 5. Mean differences, and confidence intervals, from 7 randomized controlled trials comparing mean change in triglycerides between metformin treatment and placebo.



Supplementary Figure 5. Risk ratios, and confidence intervals, from 4 randomized controlled trials comparing the risk for liver toxicity between metformin treatment and placebo.