Efficacy and Safety of Metformin for Obesity: A Systematic Review

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abstract

CONTEXT: The efficacy and safety of metformin for obesity in children and adolescents remains unclear.

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

DATA SOURCES: Data sources included PubMed, Embase, the Cochrane Library, Scopus, and ClincalTrials.gov (inception to November 2019).

STUDY SELECTION: We selected randomized controlled trials (RCTs) in which researchers assessed the efficacy and safety of metformin with lifestyle interventions, compared with a 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 BMI, BMI *z* score, homeostatic model assessment of insulin resistance, and gastrointestinal adverse effects.

RESULTS: Twenty-four RCTs (1623 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 vs −1.12 to 1.90), BMI *z* score (range of mean values: −0.37 to −0.03 vs −0.22 to 0.15), and homeostatic model assessment of insulin resistance (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: With this systematic review of RCTs, we suggest that metformin has modest but favorable effects on weight and insulin resistance and a tolerable safety profile among children and adolescents with obesity.

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To cite: Masarwa R, Brunetti VC, Aloe S, et al. Efficacy and Safety of Metformin for Obesity: A Systematic Review. *Pediatrics.* 2021;147(3):e20201610

Approximately 43 million children worldwide have overweight, and 92 million are considered to be at risk for having overweight.[1] The US Centers for Disease Control and Prevention defines a BMI in the >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 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 in those aged <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 revealed promising short-term (≤6 months) results regarding weight loss and homeostatic model assessment of insulin resistance (HOMA-IR) levels with metformin compared with a placebo and lifestyle interventions.[12–14] However, other studies revealed 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 end points.[15–19] Therefore, we conducted a systematic review to assess the efficacy and safety of metformin with lifestyle interventions, compared with a placebo with lifestyle intervention, in children and adolescents with obesity, focusing on BMI, insulin resistance, and gastrointestinal (GI) adverse effects.

METHODS

Protocol Information

In our systematic review, we followed a prespecified protocol, which was registered on PROSPERO (identifier CRD42019126099). Results are reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (Supplemental Information).[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 in which metformin with or without lifestyle interventions was compared with a placebo with or without lifestyle interventions in children and adolescents (0–19 years) with obesity (with and without insulin resistance), prediabetes, or nonalcoholic fatty liver disease (NAFLD), defined by a liver biopsy specimen with >5% steatosis within a 6-month period. We updated the search in November 2019. Medical Subject Headings terms were used in PubMed and the Cochrane Library, and Emtree terms were used in Embase. There were no language restrictions. The detailed search strategy is available in the Supplemental Information. 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 conducted in Rayyan (Qatar Computing Research Institute, Doha, Qatar).[22] The titles and abstracts were screened independently by 2 reviewers (R.M. and S.A.), 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 (V.C.B.). We restricted inclusion to RCTs in which metformin with lifestyle interventions was compared with a placebo with lifestyle interventions; lifestyle intervention represents the current standard of care for obesity in this population.[2,8] We included RCTs if any of the following was reported: BMI, BMI *z* score, body weight (in kilograms), fasting plasma glucose (FPG) level (in milligrams per deciliter), HOMA-IR, waist circumference (in centimeters), total cholesterol level (in milligrams per deciliter), triglyceride level (in milligrams per deciliter), GI adverse effects (ie, nausea, vomiting, diarrhea, abdominal pain, loose stool), and hepatic toxicity, defined as abnormal results on liver function tests. The mean change from baseline in BMI, BMI *z* score, and HOMA-IR and the incidence of GI adverse effects were the primary end points. Although our prespecified 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 in 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 (R.M. and either S.A. or V.C.B.) extracted data using a standardized form. For each trial, the following data were extracted: publication year, location, number of randomly assigned 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 end points 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 by using the Cochrane Collaboration's tool for assessing risk of bias (RoB 2; Cochrane Collaboration, London, United Kingdom).[23] The tool is structured into 5 domains through which bias may be introduced. The 5 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 of BMI and BMI *z* score. Each domain was assigned a high, low, or unclear risk of bias. Two reviewers (R.M. and V.C.B.) assessed quality independently, with disagreements adjudicated by a third reviewer (K.B.F.).

Transformation Methods for Standardized Metrics

The mean difference from baseline and SD for each treatment arm were extracted for continuous outcomes. The mean difference from baseline and SD for studies in which continuous outcomes were reported as mean and SE or 95% confidence interval (CI), median and interquartile range, or median, minimal, and maximal value were estimated by using the method described by Hozo et al[24]. Version 3.5.3 of the R Environment (R Foundation for Statistical Computing, Vienna, Austria) was used to construct forest plots to graphically present study-specific treatment effects.

RESULTS

Search Results

Our systematic search is described in Fig 1. Our systematic search yielded 2799 citations, of which 70 citations were considered for full-text review. Twenty-four RCTs were included in the systematic review, with absolute values for continuous outcomes reported in 8 RCTs and mean changes from baseline for continuous outcomes or rates of adverse effects reported in 16 RCTs.

Study and Patient Characteristics

Study characteristics of RCTs are summarized in Table 1 and Supplemental Table 4. In the 24 included RCTs, 1623 (range: 16 to 151) children and adolescents were randomly assigned to metformin (861 participants) or a 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 cointervention 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, and loose stool and were

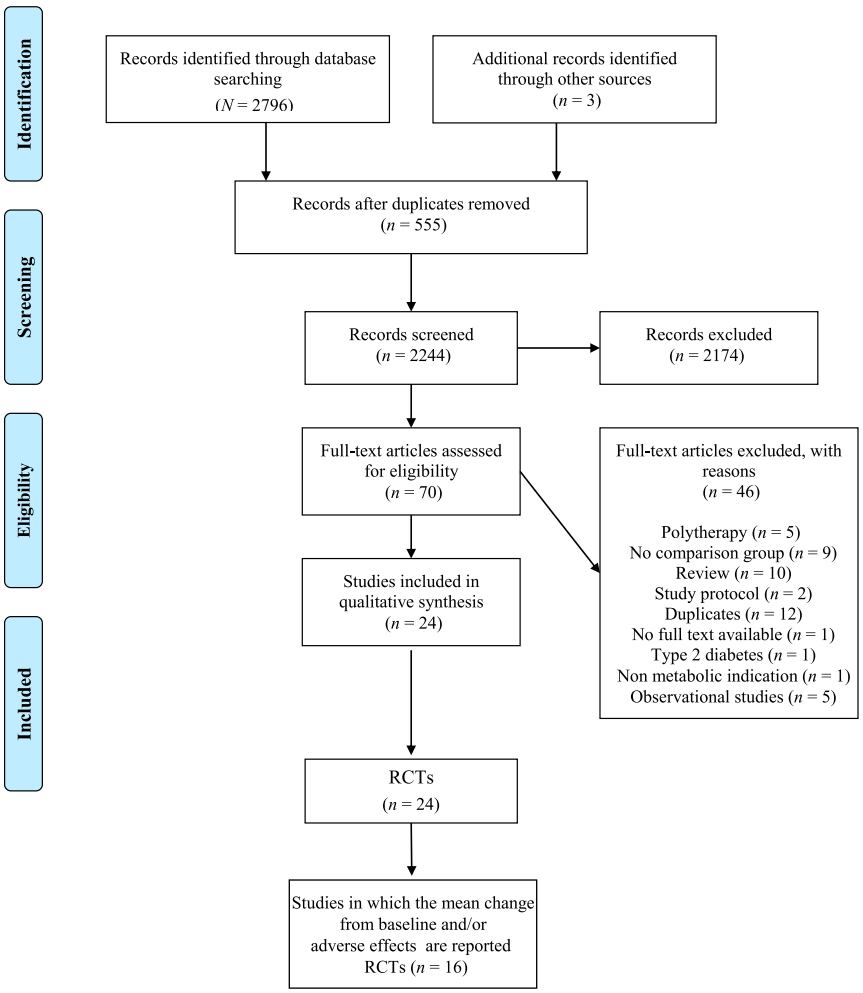

FIGURE 1
Preferred Reporting Items for Systematic Reviews and Meta-Analysis flow diagram describing study selection process for a systematic review of trials in which the efficacy and safety of metformin is assessed among children and adolescents with obesity.

TABLE 1 Characteristics of RCTs in Which Metformin Is Examined in Children and Youth

Study, y	Study Design	Location	Treatment Arms (No. Patients Randomly Assigned)	Control Arm (No. Patients Randomly Assigned)	Indication for Metformin, Age	Follow-up, mo	End Points and Side Effects
Warnakulasuriya et al,[41] 2018	Triple-blind RCT	Sri Lanka	Metformin 500–1000 mg BID + structured diet + physical activity (68)	Placebo + structured diet + physical activity (82)	Uncomplicated obesity, 8–16 y (prepubertal + pubertal)	12	BMI, wt, WC, FPG, HOMA-IR, total cholesterol, triglycerides, GI side effects, AST, ALT
Garibay-Nieto et al,[29] 2017	Double-blind RCT	Mexico	Metformin 1 g/d + lifestyle intervention (14)	Placebo + lifestyle intervention (17)	Uncomplicated obesity, 8–18 y (prepubertal + pubertal + postpubertal)	4	BMI, wt, WC, HOMA-IR, triglycerides
Pastor-Villaescusa et al,[40] 2017	Double-blind RCT	Spain	Metformin 500 mg BID + diet (68)	Placebo + diet (72)	Uncomplicated obesity, 7–14 y (prepubertal + pubertal	6	BMI, wt, FPG, HOMA-IR, total cholesterol, triglycerides, GI side effects
van der Aa et al,[33] 2016	Double-blind RCT	Netherlands	Metformin 2000 mg/d + dietary diary (23)	Placebo + dietary diary (19)	Obesity with insulin resistance, 10–16 y (prepubertal + pubertal + postpubertal)	18	BMI, wt, HOMA-IR, HbA1c, GI side effects, liver toxicity
Clarson et al,[27] 2014	RCT	Canada	Metformin XR 500–2000 mg QD + lifestyle changes (50)	Placebo QD + lifestyle changes (59)	Uncomplicated obesity, 10–16 y (prepubertal + pubertal + postpubertal)	12	BMI, GI side effects, liver toxicity
Evia-Viscarra et al,[12] 2012	Double-blind RCT	Mexico	Metformin 500 mg BID (14)	Placebo (12)	Uncomplicated obesity, 9–18 y (pubertal + postpubertal)	3	BMI, wt, WC, FPG, GI side effects, liver toxicity
Gómez-Díaz et al,[13] 2012	Double-blind RCT	Mexico	Metformin 850 mg BID + diet + exercise (28)	Placebo + diet + exercise (24)	Prediabetes, 4–17 y (prepubertal + pubertal + postpubertal)	3	BMI, wt, WC, HOMA-IR, HbA1c, GI side effects, AST, ALT
Kendall et al,[14] 2013	Double-blind RCT	United Kingdom	Metformin 1000 and 500 mg QD + diet and exercise counseling (74)	Placebo + diet and exercise counseling (77)	Prediabetes, 8–18 y (prepubertal + pubertal + postpubertal)	6	BMI, wt, FPG, HOMA-IR, total cholesterol, triglycerides, GI side effects
Mauras et al,[30] 2012	RCT ITT	United States	Metformin 500–1000 mg BID + lifestyle intervention (35)	Placebo + lifestyle intervention (31)	Uncomplicated obesity, 7–18 y (prepubertal + pubertal + postpubertal)	6	BMI, wt, WC, HOMA-IR
Lavine et al,[39] 2011	Double-blind, double-dummy RCT	United States	Metformin 500 mg BID + diet and exercise counseling (57)	Placebo + diet and exercise counseling (58)	NAFLD, 8–17 y (prepubertal + pubertal)	24	BMI, wt, WC, FPG, HOMA-IR, total cholesterol, triglycerides, liver toxicity, ALT, AST
Rynders et al,[19] 2012	RCT	United States	Metformin 500–1000 mg BID + diet + exercise (7)	No placebo; diet + exercise (9)	Uncomplicated obesity, 10–17 y (pubertal + postpubertal)	6	BMI, wt
Yanovski et al,[42] 2011	Double-blind RCT	United States	Metformin 1000 mg BID + diet (53)	Placebo + diet (47)	Obesity with insulin resistance, 6–12 y (prepubertal + pubertal)	6	BMI, wt, WC, FPG, HOMA-IR, total cholesterol, triglycerides, GI side effects, AST, ALT, vitamin B_{12}
Rezvanian et al,[31] 2010	Triple-masked RCT	Iran	Metformin 1500 mg/d + diet + exercise (41)	Placebo + diet + exercise (42)	Uncomplicated obesity, 10–18 y (prepubertal + pubertal + postpubertal)	6	BMI, WC, GI side effects
Wiegand et al,[38] 2010	RCT	Germany and Switzerland	Metformin 500 mg BID + diet (36)	Placebo + diet (34)	Prediabetes, 14–16 y (pubertal + postpubertal)	6	Wt, FPG, HOMA-IR, total cholesterol, triglycerides, GI side effects
Wilson et al,[34] 2010	Double-blind RCT	United States	Metformin XR 2000 mg QD + lifestyle intervention (39)	Placebo + lifestyle intervention (38)	Uncomplicated obesity, 13–18 y (pubertal + postpubertal)	12	BMI, HOMA-IR, total cholesterol, triglycerides, GI side effects
Clarson et al,[28] 2009	RCT	Canada	Metformin 1500 mg QD + lifestyle intervention (14)	Lifestyle intervention alone (11)	Obesity with insulin resistance, 10–16 y (prepubertal + pubertal + postpubertal)	6	BMI, FPG, triglycerides
Nadeau et al,[37] 2009	Double-blind RCT	United States	Metformin 850 mg BID + wellness education (37)	Placebo + wellness education (13)	NAFLD, 12–18 y (pubertal + postpubertal)	6	BMI, wt, FPG, total cholesterol, triglycerides, GI side effects, AST, ALT

TABLE 1 Continued

Study, y	Study Design	Location	Treatment Arms (No. Patients Randomly Assigned)	Control Arm (No. Patients Randomly Assigned)	Indication for Metformin, Age	Follow-up, mo	End Points and Side Effects
Atabek and Pirgon,[17] 2008	Double-blind RCT	Turkey	Metformin 500 mg BID + diet + exercise (90)	Placebo 500 mg BID + diet + exercise (30)	Obesity with insulin resistance, 8–16 y (prepubertal + pubertal)	6	BMI, wt, HOMA-IR, total cholesterol, triglycerides, GI side effects
Burgert et al,[15] 2008	Double-blind RCT	United States	Metformin 1500 mg/d + lifestyle counseling (15)	Placebo + lifestyle counseling (17)	Obesity with insulin resistance, 13–18 y (pubertal + postpubertal)	4	BMI, wt, FPG, HOMA-IR, total cholesterol, triglycerides
Love-Osborne et al,[36] 2008	Double-blind RCT	United States	Metformin 850 mg BID + diet + exercise (48)	Placebo + diet + exercise (16)	Obesity with insulin resistance, 12–19 y (pubertal + postpubertal)	6	BMI, GI side effects
Freemark,[25] 2007	Double-blind RCT	United States	Metformin 500 mg BID (14)	Placebo (15)	Obesity with insulin resistance, 12–19 y (pubertal + postpubertal)	6	GI side effects, AST, ALT
Srinivasan et al,[32] 2006	RCT	Australia	Metformin 1000 mg BID (10)	Placebo (12)	Obesity with insulin resistance 9–18 y, (prepubertal + pubertal + postpubertal)	6	GI side effects
Kay et al,[35] 2001	Double-blind RCT	United States	Metformin 850 mg BID + low-calorie diet (12)	Placebo + low-calorie diet (12)	Obesity uncomplicated, 14–16 y (pubertal + postpubertal)	2	Wt, FPG, total cholesterol, triglycerides, GI side effects
Freemark and Bursey,[26] 2001	Double-blind RCT	United States	Metformin 500 mg BID (14)	Placebo (15)	Obesity with insulin resistance, 12–19 y (pubertal + postpubertal)	6	BMI, FPG, HOMA-IR, HbA1c, total cholesterol, triglycerides, GI side effects

ALT, alanine transaminase; AST, aspartate transaminase; BID, twice daily; HbA1c, hemoglobin A1c; ITT, intention-to-treat analysis; QD, once daily; WC, waist circumference; XR, extended release.

reported in 16 RCTs overall. The total daily dose of metformin ranged from 500 to 2000 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 (Supplemental Table 5). 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 the authors of 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 randomly assigned to metformin and from 5% to 50% among those randomly assigned to a placebo.

Efficacy

The effect of metformin on our primary efficacy outcomes is reported in Table 2. Among the 14 RCTs in which BMI was reported, metformin was modestly efficacious at decreasing BMI (range of mean changes: −2.70 to 1.30) compared with a placebo (range of mean changes: −1.12 to 1.90). 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 (Fig 2). Furthermore, the mean change in BMI was not larger in studies that included children with a higher mean BMI at baseline. Importantly, the authors of many RCTs reported variable treatment effects, preventing definitive conclusions from being drawn from individual trials. Among the 7 RCTs in which BMI *z* score was reported, metformin consistently resulted in a decrease in the BMI *z* score (range of mean changes: −0.37 to −0.03) compared with a placebo (range of mean changes: −0.22 to 0.15) (Fig 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 (Fig 3). The largest decrease in BMI *z* score was observed in children and adolescents with NAFLD.[39] In addition, among 11 RCTs in which insulin resistance was examined, metformin resulted in modest but favorable effects on insulin resistance (range of mean changes: −3.74 to 1.00) compared with a 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 (Fig 4). Although heterogeneity was present, metformin appeared to reduce HOMA-IR in 8 RCTs; as with BMI, some trials were inconclusive because of wide 95% CIs (Fig 4).

Compared with a placebo, metformin had heterogeneous effects on other efficacy end points. Among 7 RCTs, metformin was associated with greater weight loss (range of mean changes: −5.1 to 12 kg) compared with a placebo (range of mean changes: −1.7 to 12.7 kg), resulting in an overall decrease in weight in 6 RCTs (Supplemental Fig 6). Metformin's effects on waist circumference, FPG, total cholesterol, or triglycerides were heterogeneous and inconclusive (Supplemental Figs 6–10).

Safety

In 16 RCTs, authors reported adverse effects during follow-up. Metformin treatment was associated with a higher report rate of adverse GI effects (rate range: 2% to 74%)

TABLE 2 Obesity Measures and Insulin Resistance at Maximum Follow-up in RCTs in Which Metformin Is Examined in Children and Youth

Study, y	Follow-up, mo	BMI, Mean ± SD		BMI *z* Score, Mean ± SD		HOMA-IR, Mean ± SD	
		Baseline	Mean Change	Baseline	Mean Change	Baseline	Mean Change
Warnakulasuriya et al,[41] 2018	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,[33] 2016	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,[12] 2012	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
Gómez-Díaz et al,[13] 2012	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,[30] 2012	6						
Metformin (*n* = 35)		32.00 ± 1.00	−2.40 ± 2.95	NA	NA	4.80 ± 0.40	0.34 ± 4.49
Placebo (*n* = 31)		33.20 ± 0.70	−1.12 ± 2.78	NA	NA	5.20 ± 0.60	1.6 ± 4.45
Lavine et al,[39] 2011	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,[19] 2012	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,[42] 2011	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,[31] 2010	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,[38] 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 (*n* = 29)		32.93 ± 6.56	0.07 ± 0.51	2.79 ± 0.60	−0.02 ± 0.07	4.58 ± 3.00	NA
Wilson et al,[34] 2010	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,[28] 2009	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 and Pirgon,[17] 2008	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,[15] 2008	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,[36] 2008	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

NA, not available.

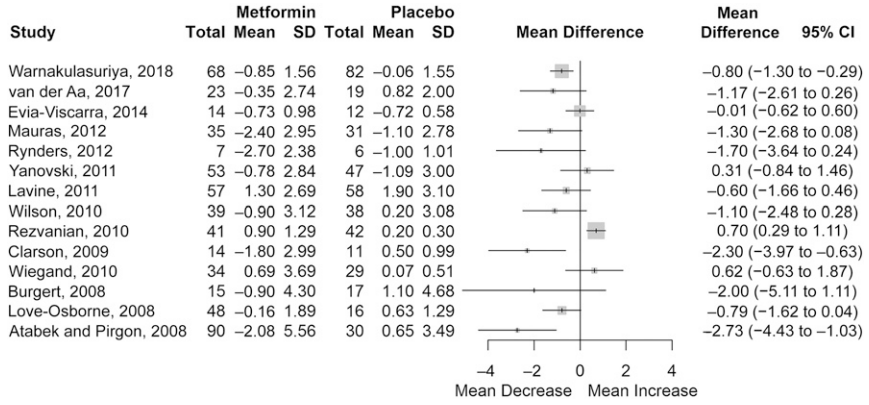

FIGURE 2

Mean differences and CIs from 14 RCTs in which change in BMI was compared between metformin treatment and a placebo among children and adolescents with obesity.

compared with a placebo (rate range: 0% to 42%) (Table 3, Fig 5). Evidence regarding a potential increased risk of liver toxicity was inconclusive, with potential liver toxicity reported in only 4 RCTs and heterogeneous results across studies (Supplemental Fig 11). Adverse effects were not stratified by ethnicity in the included RCTs. The occurrence of adverse effects was not reported in 7 RCTs, with 6 studies conducted in the United States and 1 study conducted in Mexico.

DISCUSSION

Our study was designed to examine the efficacy and safety of metformin with lifestyle interventions, compared with a 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 a 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 with a 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 in these previous knowledge syntheses, researchers examined metformin therapy for insulin resistance and obesity in children and adolescents, they had important methodologic limitations. In these syntheses, which included 1 recent meta-analysis,[46] several systematic reviews, and 1 older meta-analysis,[43–45,47] researchers focused on absolute BMI, did not examine BMI *z* score, and did not assess safety outcomes. In the meta-analyses, data were pooled across trials despite substantial heterogeneity in mean age across studies and substantial loss to follow-up.[45–47] Moreover, the authors 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 end point, 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

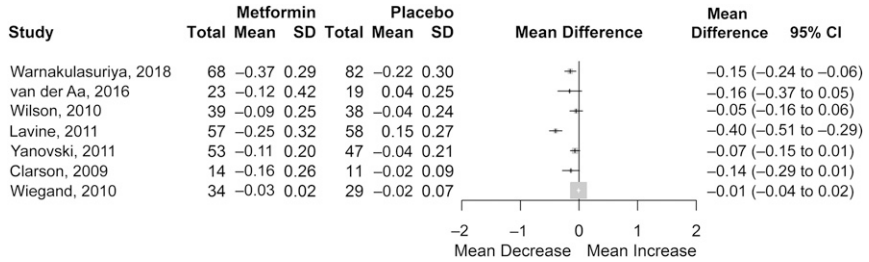

FIGURE 3

Mean differences and CIs from 7 RCTs in which change in BMI *z* score is compared between metformin treatment and a placebo among children and adolescents with obesity.

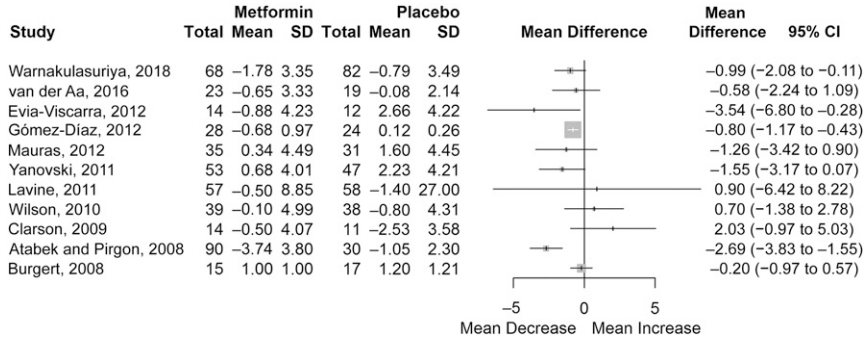

FIGURE 4

Mean differences and CIs from 11 RCTs in which mean change in HOMA-IR is compared between metformin treatment and a placebo among children and adolescents with obesity.

and adolescents because 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 in which changes in the BMI *z* score were reported revealed 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 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 as well as other measures of adiposity, such as insulin resistance; FPG; waist circumference adjusted for age, sex, and height; and the lipid profile.

Insulin resistance measured by HOMA-IR decreased in the metformin treatment arm, indicating modest efficacy. However, these changes must be interpreted carefully because changes in insulin resistance may be different among school-aged children and adolescents because of their different stages of pubertal development and changes in other hormones.[51] The majority of trials included prepubertal and pubertal children and adolescents, but results were not stratified by age or developmental stage. The measurement of developmental stage varied, assessed by either a trained endocrinologist and/or 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

TABLE 3 GI Adverse Effects Reported During Follow-up in RCTs in Which Metformin Is Examined in Children and Youth

Study, y	Follow-up, mo	Daily Dose, mg	GI Adverse Effects Reported	Metformin Cases/n (%)	Placebo Cases/n (%)
Warnakulasuriya et al,[41] 2018	12	1000–2000	GI adverse effects and anorexia	25/68 (37)	22/82 (27)
Pastor-Villaescusa et al,[40] 2017	6	1000	Diarrhea	9/68 (13)	6/72 (8)
van der Aa et al,[33] 2016	18	2000	Nausea and diarrhea	17/23 (74)	8/19 (42)
Clarson et al,[27] 2014	12	500–2000	Diarrhea	1/50 (2)	0/59 (0)
Evia-Viscarra et al,[12] 2012	5	1000	Epigastric pain	2/14 (14)	1/12 (8)
Gómez-Díaz et al,[13] 2012	3	1700	Diarrhea	10/28 (36)	0/24 (0)
Kendall et al,[14] 2013	6	500 or 1000	Diarrhea, nausea, abdominal pain	20/74 (27)	8/77 (10)
Yanovski et al,[42] 2011	6	2000	Loose stool, vomiting	21/53 (40)	8/47 (17)
Rezvanian et al,[31] 2010	6	1500	Abdominal pain, loose stool	3/41 (7)	0/42 (0)
Wiegand et al,[38] 2010	6	1000	GI adverse effects	5/36 (14)	9/34 (26)
Wilson et al,[34] 2010	12	2000	Nausea, vomiting	9/39 (23)	3/38 (8)
Nadeau et al,[37] 2009	6	1700	Nausea, diarrhea, abdominal pain	10/37 (27)	3/13 (23)
Atabek and Pirgon,[17] 2008	6	1000	Vomiting	2/90 (2)	0/30 (0)
Love-Osborne et al,[36] 2008	6	1700	GI adverse effects	14/48 (29)	3/16 (19)
Srinivasan et al,[32] 2006	6	2000	Nausea	2/10 (20)	0/12 (0)
Kay et al,[35] 2001	2	1700	Nausea, loose stool	5/12 (42)	0/12 (0)

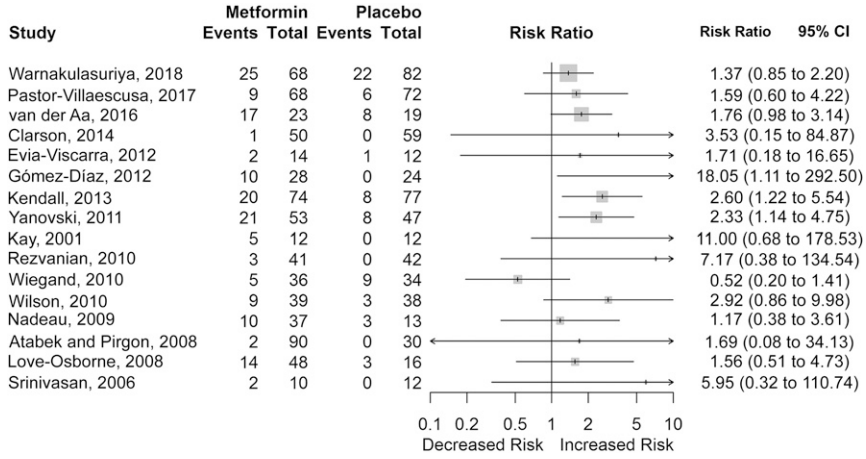

FIGURE 5

Risk ratios and CIs from 16 RCTs in which risk of GI adverse effects is compared between metformin treatment and a placebo among children and adolescents with obesity.

insulin resistance was consistent only among individuals with NAFLD; however, the trial of patients with NAFLD had a 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 in which researchers assessed changes in the FPG level, waist circumference, and lipid profile was small. For the FPG level, the studies revealed an overall decrease, whereas the effects on waist circumference and the lipid profile were heterogeneous and inconclusive. In most trials, the 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, comedications, 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 with lifestyle interventions and a 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 aged ≥60 years, less effective than metformin in adults aged 45 to 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, the efficacy of metformin in children and adolescents with prediabetes was assessed in 3 RCTs.[13,14,38] These trials revealed a modest decrease in the BMI *z* score and no change in insulin resistance and the FPG level, suggesting that metformin is not as effective in the treatment of prediabetes in children and adolescents. In children and adolescents, prediabetes is often a transient condition, and the determinants of progression to overt 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 to prevent the progression to overt type 2 diabetes.

Generally, in adults and adolescents, clinically significant responses to metformin are not seen at doses <1500 to 2000 mg/day among patients with type 2 diabetes.[57] The metformin dose used in trials included in our systematic review ranged from 500 to 2000 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 of up to 1000 mg/day as opposed to doses of 1500 to 2000 mg/day. However, included trials had relatively high rates of loss to follow-up (5% to 80% among patients randomly assigned to metformin), and authors did not report the specific doses of metformin at which patients had discontinued use because of GI adverse effects.

Our study has several potential limitations. First, we aimed to assess high-quality evidence from RCTs, and although our systematic review included 24 RCTs, changes from baseline were not reported in many, preventing the assessment of treatment effects of metformin for many studies. We focused on assessing the mean change and its variance from baseline. Although 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 a meta-analysis. Third, for most of our secondary end points, there was substantial heterogeneity in observed treatment effects, and results were inconclusive for waist circumference, FPG, the lipid profile,

and liver toxicity. Fourth, in the studies, loss to follow-up ranged between 5% and 80% in the metformin arm and between 5% and 50% in the placebo arm. Although the authors of most studies reported similar drop-out rates across treatment arms, drop-out analyses were conducted in only 3 studies.[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 reveals 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 regimen. 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 could 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 revealed smaller treatment effects, suggesting some uncertainty in its benefits. Nonetheless, metformin may be considered for use as a pharmacologic therapy in this pediatric population because of its modest efficacy, availability, cost, and safety profile. Future RCTs with standardized lifestyle interventions and real-world studies are required to characterize pediatric patients who may benefit most from metformin monotherapy and metformin in combination with other drugs for the treatment of insulin resistance and obesity.

ABBREVIATIONS

CI: confidence interval
FPG: fasting plasma glucose
GI: gastrointestinal
HOMA-IR: homeostatic model assessment of insulin resistance
NAFLD: nonalcoholic fatty liver disease
RCT: randomized controlled trial

This trial has been registered with PROSPERO (https://www.crd.york.ac.uk/prospero/) (identifier CRD42019126099).

DOI: https://doi.org/10.1542/peds.2020-1610

Accepted for publication Oct 30, 2020

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: Dr Masarwa is supported by a postdoctoral bursary from the Fonds de Recherche du Québec – Santé (Quebec Foundation for Health Research) and a training stipend from the Canadian Institutes of Health Research Drug Safety and Effectiveness Cross-Disciplinary Training Program. Ms Brunetti is supported by a doctoral bursary from the Fonds de Recherche du Québec – Santé and a Drug Safety and Effectiveness Cross-Disciplinary Training award. Dr Henderson is supported by a junior II salary support award from the Fonds de Recherche du Québec – Santé. Dr Filion is supported by a senior salary support award from the Fonds de Recherche du Québec – Santé and a William Dawson Scholar award from McGill University.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

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Pediatrics originally published online February 19, 2021;

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