CHILDHOOD OBESITY
Month 2020 | Volume X, Number X

DOI: 10.1089/chi.2019.0040

ORIGINAL ARTICLE

Metformin Therapy Reduces Obesity Indices in Children and Adolescents: A Systematic Review and Meta-Analysis of Randomized Clinical Trials

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Abstract

Purpose: Few studies have summarized findings for the effect of metformin on obesity indices. Therefore, we aimed to conduct a systematic review and meta-analysis on the effect of metformin on obesity indices among children and adolescents.

Methods: Relevant articles published up to September 2018 were searched in SCOPUS, Medline, and Google Scholar using appropriate keywords. All clinical trials that examined the effect of metformin on obesity indices in children and adolescents were included.

Results: Overall, 38 studies, including 2199 participants (39.75% male and 60.25% female), were included. The pooled results indicated that metformin significantly reduced BMI [weighted mean difference (WMD): −1.07 kg/m^2; 95% confidence interval (CI): −1.43 to −0.72]. Same findings were found for waist circumference (WC) (WMD: −1.93 cm; 95% CI: −2.69 to −1.16). Metformin also reduced body weight in all participants (WMD: −2.51 kg; 95% CI: −3.14 to −1.89). Moreover, it reduced body fat mass in patients with overweight or obesity (WMD: −1.90%; 95% CI: −3.25 to −0.56) and chronic diseases (WMD: −1.41%; 95% CI: −2.23 to −0.58), but not among those with growth problems. Metformin therapy did not affect lean body mass (LBM) in patients with overweight or obesity and growth problems; however, it reduced LBM in patients with chronic diseases (WMD: −1.49 kg; 95% CI: −2.69 to −0.30).

Conclusions: We found a significant reduction in BMI, body weight, WC, and fat mass following administration with metformin. However, the effect of metformin on LBM was not significant. Further studies are required to confirm these findings.

Keywords: adolescent; children; metformin; obesity; weight

Introduction

Overweight and obesity are common public health problems among children and adolescents.[1] It has been suggested that teens with overweight and obesity often become obese adults in future.[2,3] Moreover, childhood obesity is associated with an elevated risk of chronic disorders, including hypertension, hyperlipidemia, and high blood pressure, as well as other chronic diseases, such as diabetes, cardiovascular diseases, and several cancers.[4] Cumulative studies have shown that the prevalence of overweight and obesity in children and adolescents has increased substantially such that twenty-three ·8% of boys and twenty-two ·6% of girls in developed countries and twelve ·9% of boys and thirteen ·4% of girls in developing countries were overweight or obese in 2013.[5]

Along with common recommendations for making changes in lifestyle, some therapeutic strategies are also used in the treatment of overweight and obesity in these age groups.[6] Metformin is a glucose-lowering drug commonly used by diabetic patients.[7] However, recent studies

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have shown other therapeutic effects of this popular drug.[8] Although some studies have found a significant reduction in obesity indices after administration with metformin,[9,10] other studies failed to find such an effect.[11,12] A systematic review in 2009 showed that intake of metformin comparing with placebo reduced BMI in obese subjects aged ≤19 years.[13] In addition, a recent meta-analysis also has shown a significant reduction in BMI after adding metformin to insulin therapy in type 1 diabetes mellitus children.[14] Metformin therapy also significantly reduced body weight in patients who received antipsychotic drugs, as found in another meta-analysis.[15]

To our knowledge, research on the effect of metformin therapy on obesity indices is limited. Most available review studies in this area have focused on some specific obesity indices. Moreover, those studies have been considerably conducted among adults with different health conditions. Therefore, we aimed at conducting a meta analysis to summarize the effect of metformin on obesity indices among children and adolescents.

Methods

Search Strategy

All relevant clinical trials published up to September 2018 were searched in SCOPUS (www.scopus.com), Medline (www.ncbi.nlm.nih.gov/PubMed), and Google Scholar databases, without restrictions for language or publication date. We used the following search terms in our search: (''Metformin''[tiab] OR ''Metformin''[Mesh]) AND (''body weight''[tiab] OR ''obesity''[tiab] OR ''body fat''[tiab] OR obese[tiab] OR overweight[tiab] OR ''body mass index''[tiab] OR BMI[tiab] OR Adiposity[tiab] OR Anthropometry[tiab] OR ''abdominal obesity''[tiab] OR ''waist circumference''[tiab] OR ''waist-to-hip ratio''[tiab] OR ''waist-to-height ratio''[tiab] OR WHR[tiab] OR ''hip circumference''[tiab] OR ''weight change''[tiab] OR ''weight loss''[tiab] OR ''Waist-Hip Ratio''[Mesh] OR ''Waist Circumference''[Mesh] OR ''Obesity, Abdominal''[Mesh] OR ''Anthropometry''[Mesh] OR ''Adiposity''[Mesh] OR ''Body Weight''[Mesh] OR ''Body Mass Index''[Mesh] OR ''Overweight''[Mesh] OR ''Obesity''[Mesh] OR ''Obesity, Abdominal''[Mesh] OR ''Body Composition''[Mesh] OR ''Body Weight Changes''[Mesh]).

In addition, we manually reviewed reference lists of recruited articles, as well as relevant systematic reviews and meta-analyses. Cochrane handbook for systematic reviews of interventional studies and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed throughout the study.

Eligibility Criteria

We included all the clinical trials that met the following criteria: (i) were randomized controlled trials with parallel design; (ii) were performed on children or adolescents (aged 18 years old or younger); and (iii) examined body weight (BW), BMI, waist circumference (WC), fat mass (FM), and lean body mass (LBM) as outcomes of interest. Studies were excluded if they were conducted in adults or animal studies, had no random allocation or control group, had an observational design, or used other interventions along with metformin therapy. Moreover, we did not include gray literature, letters, case reports, reviews, and crossover trials in this study. If several publications reported data from the same population, a study with the largest sample size or duration was included.

Data Extraction

Two investigators (A.S. and S.M.M.) independently obtained necessary data from included studies. The following information was extracted from each study: first author's name, country, journal details, year of publication, study design, participant characteristics (age, gender, number of participants in each group), and intervention characteristics (including metformin dosage and duration of exposure). Mean ± SD (standard deviation) of obesity indices at study baseline and end of intervention or changes between pre- and postintervention were recruited. When a study had reported data on several points during the intervention period, we get data from the latest measures. Moreover, if a investigation had used metformin in different dosages, data for each dosage in comparison to placebo were considered as a separate study.

Quantitative Data Synthesis and Statistical Analyses

The overall effect size was calculated using mean (SD) change of study outcomes. In a study that did not report SD for changes, we calculated it using the following formula: $SD = \text{square root } [(SD_{\text{pre-treatment}})^2 + (SD_{\text{post-treatment}})^2 - (2R \times SD_{\text{pre-treatment}} \times SD_{\text{post-treatment}})]$, assuming a correlation coefficient (R) of 0.9. The standard error of the mean (SEM) was converted to SD using the following formula: $SD = SEM \times \sqrt{n}$ (n is the number of subjects). Moreover, median and ranges or 95% confidence intervals (CIs) were also converted to SDs using the method described by Hozo et al.[16]

The random-effects model was used to calculate the overall effect sizes. Between-study heterogeneity was examined using Cochran's Q-test (significance set at $p < 0.1$) and I^2 statistics. To find sources of heterogeneity, we performed subgroup analyses based on participant's health status (subjects with chronic diseases, growth problems, and psychological disorders), study design (with and without placebo), participants' age (<10, 10–15, and ≥15 years) and gender (female or both), metformin dosage (<1000, 1000–1500, 1500–2000, and >2000 mg/day), and duration of study (<6 months, 6 months to 1 year, and ≥1 year). A sensitivity analysis was done to find if specific research had a significant influence on overall findings. Publication bias was assessed by visual inspection of funnel plots, confirmed by Egger's regression test. Statistical analyses were done using STATA software (version 14.0; StataCorp, College Station, TX). p-Values <0.05 were considered as statistically significant.

Results

Study Characteristics

Flow diagram of study selection is presented in Figure 1. Overall, 38 randomized controlled trials (RCTs), which had rolled 2199 participants (39.75% male and 60.25% female), including 1128 patients in metformin and 1071 patients in control groups, with a mean age of 13.66 years, were included.[10–12,17–51] Characteristics of these studies are presented in Table 1. All included studies were written in English and published between 2001 and 2017. Among these 38 included studies, 10 studies were done in Europe,[12,20,23,25,31,34,42,44,48,49] 20 in the United States and Canada,[10,17,18,21,22,24,29,30,33,35,36,39–41,43,45,47,50,51] 3 in Middle America,[11,27,28] 1 in Africa (Egypt),[26] and the remaining 2 studies in Asia (Iran).[19,46] In addition, two studies were done among populations from different countries.[32,37] Out of included studies, 12 studies were performed in children[17,25,27,28,31,32,39,40,42,44–46,51] and 25 studies in adolescents.[10–12,18–24,26,29,30,33–38,41,43,47–50] In addition, six studies were conducted in female participants,[21,26,30,31,44,47] while the others recruited participants from both genders.[10–12,17–20,22–25,27–29,32–43,45,46,48–51] Among included studies, one study had an open-label design.[42] Control groups received no intervention,[26,31,39,44] placebo,[10–12,17–23,25,27–30,32–38,41,43,45–51] and diet or exercise[24,39,40,42] in these studies. Participants of these studies had obesity[11,17,20,22,24,27,33,34,40,43,45–51] or diabetes,[10,12,29,32,37,41] other chronic diseases (including nonalcoholic fatty liver disease and polycystic ovary syndrome),[21,25,26,28,30,31,36,38,39,42,44] or psychiatric disorders (including schizophrenia and autism spectrum disorder).[18,19,23,35]

Metformin capsules were used in dosages ranged between 0.5 and 3 g/day in these studies. Moreover, duration of intervention was varied from 12 to 192 weeks. Among included studies, 28 studies measured participants' body weight,[11,12,17–20,22,23,25,26–28,31–37,39–43,45,47,48,51] 36 studies measured BMI,[10–12,17–24,26–32,34–36,38–51] 16 studies measured WC,[11,12,25,27,28,30,35–37,40,41,43–46,51] 13 studies measured fat mass,[17,23,25,31,33,36,37,40,45,47,48,50,51] and the remaining 7 studies measured LBM[17,25,31,33,37,44,50] as the outcome. In addition, among studies in which fat mass was reported as the outcome, four studies measured percent of total body weight,[23,36,37,40] while the remaining studies measured total body weight in kilograms.[17,25,31,33,45,47,48,50,51] Adjustment for baseline

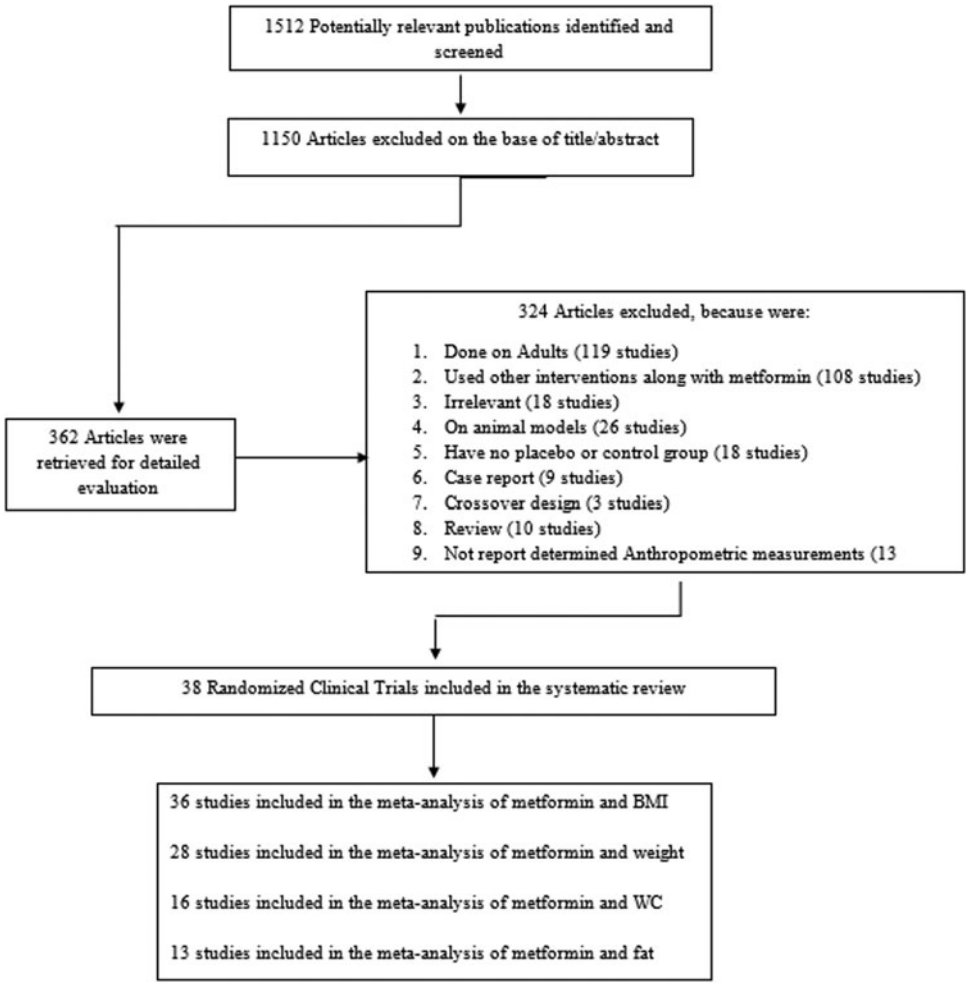

Figure 1. Flow diagram of the study selection.

Table 1. General Characteristics of Included Studies

Code/Author (year)	Subjects and gender	Age range, years Mean	RCT	Intervention type		Duration, weeks	Outcome, kg		Any other intervention (from)	Notes about subjects	Adjustment
				Intervention (name and composition)	Control (name and composition)		Intervention, mean ± SD Number	Control, mean ± SD Number			
1. Rezvanian et al. (2010)[46]	Both: 83 Metformin: 41 Placebo: 42	Metformin: 13.1 ± 1.4 Placebo: 13.4 ± 1.4	Triple masked randomized clinical trial	Intervention group received metformin, with its dosage increased weekly from 500 to 1500 mg/day.	The placebo content consisted of two commonly used filler in manufacturing of tablet and capsule: lactose and calcium phosphate.	24	BMI Changes: 0.9 ± 0.1 WC: Changes: −0.4 ± 0.03	BMI Changes: 0.2 ± 0.04 WC: Changes: −0.2 ± 0.04	Yes	Eighty-three children and adolescents, aged 10–16 years BMI equal to or greater than the age- and sex-specific 95th percentile	No
2. Wilson et al. (2010)[50]	F: 51 M: 26 Both: 77 Metformin: 39 Placebo: 35	Metformin: 14.8 ± 1.3 Placebo: 15 ± 1.5	Randomized, double-blind, placebo-controlled trial	Intervention group takes 1 tablet/d (metformin hydrochloride XR 500) orally before dinner for 2 weeks, then 2 tablets/day for 2 weeks, then 4 tablets/day from week 8 to 52.	Control group takes 1 tablet/d placebo orally before dinner for 2 weeks, then 2 tablets/day for 2 weeks, then 4 tablets/day from week 8 to 52.	52	BMI Changes: −0.9 ± 0.5 DXA fat mass: Changes: −1.0 ± 1.5 DXA lean mass: Changes: −0.1 ± 1.1	BMI Changes: 0.2 ± 05 DXA fat mass: Changes: −0.1 ± 1.1 DXA lean mass: Changes: 1.4 ± 1.1	No	Adolescents aged 13 years to younger than 18 years BMI equal to or greater than the age- and sex-specific 95th percentile but weighed less than 136 kg	Site, sex, race, ethnicity, and age
3. Evia-Viscarra et al. (2012)[11]	F: 17 M: 9 Both: 26 Metformin: 12 Placebo: 14	Metformin: 12.65 ± 1.98 Placebo: 14.12 ± 1.21	Randomized, double-blind, placebo-controlled trial	One tablet a day 500 mg of metformin. The dose was then increased to one tablet every 12 hours (total metformin dose of 1 g/day) for 3 months.	One tablet a day placebo. The dose was then increased to one tablet every 12 hours for 3 months.	12	Before int: Weight, kg: 81.21 ± 18.74 After int: Weight, kg: 80.58 ± 18.27 Before int: BMI: 33.44 ± 5.82 After int: BMI: 32.71 ± 5.77 Before int WC: 101.16 ± 13.87 After int: WC: 100.59 ± 14.6	Before int: Weight, kg: 86.26 ± 26.02 After int: Weight, kg: 85.35 ± 25.76 Before int: BMI: 32.82 ± 6.37 After int: BMI: 32.10 ± 6.52 Before int: WC: 104.50 ± 16.26 After int: WC: 101.21 ± 13.83	No	Twenty-six obese adolescents with insulin resistance, aged 9–18 years	No
4. Atabek and Pirgon (2008)[20]	F: 60 M: 60 Both: 120 Metformin: 90 Placebo: 30	Metformin: 11.83 ± 2.8 Placebo: 11.6 ± 2.7	Randomized, double-blind, placebo-controlled clinical trial	The metformin group received oral treatment with 1000 mg metformin (500 mg twice daily).	Placebo twice daily.	24	Before int: Weight, kg: 67.1 ± 16.8 After int: Weight, kg: 63.7 ± 16.9 Before int: BMI: 28.5 ± 3.4 After int: BMI: 26.7 ± 4 Change: −2.08 ± 2.32	Before int: Weight, kg: 66.2 ± 16.9 After int: Weight, kg: 69.8 ± 16.7 Before int: BMI: 28.0 ± 3.4 After int: BMI: 28.6 ± 4.2 Change: 0.65 ± 2.5	No	Ninety obese adolescents (90; 45 females and 45 males), aged 9–17 years, were recruited from among obese adolescents with hyperinsulinemia. The control group consisted of 30 obese adolescents (15 females and 15 males) with hyperinsulinemia	No
5. Arman et al. (2008)[19]	F: 11 M: 21 Both: 32 Metformin: 16 Placebo: 16	Metformin: 11.25 ± 2.46 Placebo: 8.93 ± 4.28	Randomized, double-blind, placebo-controlled clinical trial	Each subject was given a 1 week supply 500 mg metformin. After 1 week, the dose was increased to tablets.	Placebo administration was matched to metformin in identical dosing.	12	Before int: Weight, kg: 35.2 ± 12.94 After int: Weight, kg: 36.03 ± 12.81 Change: 1 ± 0.32 Before int: BMI: 17.42 ± 2.75 After int: BMI: 17.9 ± 2.63	Before int: Weight, kg: 29.83 ± 20.04 After int: Weight, kg: 32.03 ± 22.45 Change: 1.35 ± 2.4 Before int: BMI: 17.01 ± 4.42 After int: BMI: 18.11 ± 4.97	Yes	Patients with diagnosis of schizophrenia taking risperidone 2–6 mg/day	No
6. Hoeger et al. (2008)	F: 16 Metformin: 6 Placebo: 10	Metformin: 16 ± 1.7 Placebo: 15.4 ± 1.7	Randomized placebo-controlled clinical trials	Metformin was given at a dose of 1700 mg/day in divided doses of 850 mg, starting as single doses of 425 mg and building gradually to two capsules twice a day.	Lactose powder for the placebo. Placebo administration was matched to metformin in identical dosing.	24	Before int: WC: 100.5 ± 11.8 After int: WC: 105.3 ± 13.9 Before int: BMI: 35.0 ± 8.2 After int: BMI: 35.7 ± 8.6	Before int: WC: 104.7 ± 15.9 After int: WC: 105.3 ± 18.6 Before int: BMI: 34.9 ± 6.7 After int: BMI: 35.5 ± 6.8	Yes	All subjects were postmenarchal adolescent women between the ages of 12 and 18 years with BMI above the 95th percentile and evidence of menstrual irregularity and clinical or biochemical evidence of hyperandrogenism	No

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Table 1. General Characteristics of Included Studies *continued*

Code/Author (year)	Subjects and gender	Age range, years Mean	RCT	Intervention type		Duration, weeks	Outcome, kg		Any other intervention (from)	Notes about subjects	Adjustment
				Intervention (name and composition)	Control (name and composition)		Intervention, mean ± SD Number	Control, mean ± SD Number			
7. Hoeger et al. (2008)	F: 36 Metformin: 18 Placebo: 18	Metformin: 14.7±1.6 Placebo: 15.8±1.6	Randomized placebo-controlled clinical trials	Metformin or placebo was given divided into four doses. Metformin dose for this study was 2000 mg/day.	Lactose powder for the placebo. Placebo administration was matched to metformin in identical dosing.	24	Before int: WC: 110.1±10.2 After int: WC: 106.2±11.7 Before int: BMI: 34.3±4.6 After int: BMI: 32.4±4.8	Before int: WC: 111.1±8.9 After int: WC: 109.7±8.4 Before int: BMI: 35.1±4.9 After int: BMI: 33.9±4.2	Yes	All subjects were postmenarchal adolescent women between the ages of 12 and 18 years with BMI above the 95th percentile and evidence of menstrual irregularity and clinical or biochemical evidence of hyperandrogenism	No
8. Kendall et al. (2013)	F: 102 M: 49 Both: 151 Metformin: 74 Placebo: 77	Metformin: 13.68±2.3 Placebo: 13.64±2.2	Randomized, double-blind, placebo-controlled trial	Intervention group received 1.5 grams of metformin (Glucophage) every day.	Received 1.5 grams of placebo (lactose tablet) every day.	24	Before int: Weight, kg: 100.3±24.1 After int: Weight, kg: 102.7±24.8 Before int: BMI: 37.10±6.35 After int: BMI: 36.85±6.29	Before int: Weight, kg: 96.4±21.8 After int: Weight, kg: 96.8±20.8 Before int: BMI: 35.95±6.32 After int: BMI: 36.16±6.49	No	Adolescents with age range 8–18 years, BMI greater than the 98th, and impaired glucose tolerance plasma glucose value 7.8 or greater to 11.1 or hyperinsulinemia	Age, sex, pubertal status, and ethnicity
9. Lavine et al. (2011)	F: 22 M: 49 Both: 115 Metformin: 57 Placebo: 58	Metformin: 13.01±2.4 Placebo: 12.09±26	Randomized, double-blind, placebo-controlled trial	Oral metformin (500 mg twice daily).	Placebo twice daily	96	Weight, kg: Change: BMI: Change: 1.3 (0.6–2.0) CI WC: Change: 3.9 (1.7–6.2) CI Total fat %: Change: −2.4 (−3.6 to −1.2) CI	Weight, kg: Change: 12.7 (9.7–15.6) CI BMI: Change: 1.9 (1.1–2.7) CI WC: Change: 5.6 (2.5–8.6) CI Total fat %: Change: −1.9 (−3.5 to −0.3) CI	Yes	One hundred fifteen patients (aged 8–17 years) with biopsy-confirmed NAFLD conducted. Most patients were prepubertal, obese, and insulin resistant	Baseline values
10. Libman et al. (2015)	F: 92 M: 48 Both: 140 Metformin: 71 Placebo: 69	Metformin: 15.4±1.7 Placebo: 15.1±1.08	Randomized, double-blind, placebo-controlled trial	2000 mg every day.	Placebo administration was matched to metformin in identical dosing	26	Weight, kg: Change: 0.0 (0.0–0.0) WC: Change: 0 (0.76) Body fat %: Change: 0 (−1 to 1) Body fat: Change: 0 (−1 to 1) Lean, kg: Change: 0 (0 to 0)	Weight, kg: Change: 2 (2–3) WC: Change: 1 (−1 to 3) Body fat %: Change: 1 (0–1) Body fat: Change: 2 (1–2) Lean, kg: Change: 1 (0–1)	No	One hundred forty adolescents aged 12.1–19.6 years with mean type 1 diabetes duration 7.0 years, BMI 94th percentile.	Age and sex
11. Kay et al. (2001)[33]	F: 15 M: 9 Both: 22 Metformin: 12 Placebo: 12	Metformin: 15.6±0.4 Placebo: 15.7±0.5	Randomized, double-blind, placebo-controlled trial	Subjects were initially started on metformin 850 mg. After 1 week, metformin 850 mg was increased to twice daily.	Subjects were initially started placebo once daily. After 1 week, placebo dose was increased to twice daily.	12	Weight Change: −6.1±0.72 Fat free mass Change: −1.6±0.56 Body fat Change: −6±0.6	Weight Change: −3.2±0.5 Fat free mass Change: −1.8±0.32 Body fat Change: −2.7±0.51	No	Twenty-four caucasian obese adolescents with a BMI greater than 30 kg/m^2	Age, sex, baseline values, diet sequence, and feeding period.
12. Nadeau et al. (2015)[41]	Both: 74 Metformin: 37 Placebo: 37	Metformin: 15.9±1.7 Placebo: 16±1.6	Randomized, double-blind, placebo-controlled trial	1000 mg every day.	The placebo appeared identical to the metformin tablets	24	Before int: BMI: 23.5±3.0 After int: BMI: 23.5±2.4 Before int: Weight: 65.7±12.3 After int: Weight: 66.2±11.2 Before int: WC: 77.1±9.2 After int: WC: 75.1±8.4	Before int: BMI: 24.3±4.1 After int: BMI: 24.7±3.7 Before int: Weight: 67.1±13.2 After int: Weight: 68.5±11.7 Before int: WC: 76.0±8.9 After int: WC: 76.2±9.0	No	T1DM adolescents' duration of at least 1-year age between 13 and 20 years old, with HbA1c levels higher than 8.5% at the two clinic visits before the screening visit.	No

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Table 1. General Characteristics of Included Studies *continued*

Code/Author (year)	Subjects and gender	Age range, years Mean	RCT	Intervention type		Duration, weeks	Outcome, kg		Any other intervention (from)	Notes about subjects	Adjustment
				Intervention (name and composition)	Control (name and composition)		Intervention, mean ± SD Number	Control, mean ± SD Number			
13. Love-Osborne et al. (2008)[38]	F: 60 M: 25 Both: 85 Metformin: 60 Placebo: 25	Metformin: 15.5 ± 1.7 Placebo: 14.2 ± 4.6	Randomized, double-blind, placebo-controlled trial	Subjects were started on metformin 500 mg once daily. At 1 month, the dose increased to 500 mg twice daily, followed by an increase to 850 mg twice daily at 2 months.	Subjects were started on placebo 500 mg once daily. At 1 month, the dose increased to 500 mg twice daily, followed by an increase to 850 mg twice daily at 2 months.	24	BMI Change: −0.16 ± 1.89	BMI Change: 0.63 ± 1.29	No	Eighty-five adolescents with insulin resistance and BMI >95% for age.	No
14. Nobili et al. (2008)[42]	F: 17 M: 40 Both: 57 Metformin: 28 Control: 29	Metformin: 12.0 (10.7–17.8) Control: 12.07 (10.2–18.0)	An open-label, 24-month, observational pilot study	The dosage of metformin was progressively titrated from 250 to 500 mg TID, at weekly intervals.	Control group was selected from a separate but parallel study ($N = 30$) that had identical inclusion criteria on the use of antioxidants in NAFLD.	104	Before int: BMI: 25.0 (range 25.5–29.1) After int: BMI: 24.2 (range 20.3–28.4) Before int: Weight: 35 (range 21–43) After int: Weight: 32 (range 20–46)	Before int: BMI: 26.7 (range 15.2–31.4) After int: BMI: 24.1 (range 15.2–27.7) Before int: Weight: 66 (range 28–121) After int: Weight: 33 (range 14–45)	No	Patients with biopsy-proven NAFLD or nonalcoholic steatohepatitis	No
15. Ong et al. (2007)[44]	F: 22 Metformin: 10 Control: 12	Metformin: 9 ± 0.1 Control: 9.1 ± 0.1	The follow-up post-treatment discontinuation of a previously reported open-label study.	Metformin group received 850 mg once daily.	Untreated	156	Before int: BMI: 21 ± 0.8 After int: BMI: 21.6 ± 0.6 Before int: WC: 68.3 ± 2.3 After int: WC: 71.2 ± 1.5 Before int: Lean body mass: 26.6 ± 1 After int: Lean body mass: 36 ± 0.8	Before int: BMI: 20.2 ± 0.8 After int: BMI: 22.7 ± 0.5 Before int: WC: 64.3 ± 1.8 After int: Wc: 75.1 ± 1.2 Before int: Lean body mass: 25.2 ± 1.2 After int: Lean body mass: 31.8 ± 1.1	No	Twenty-two low birth-weight girls with early normal puberty (Stage 2 breast development at age 8–9 years)	Baseline values
16. Hamilton et al. (2003)[29]	F: 14 M: 13 Both: 27 Metformin: 14 placebo: 13	Metformin: 15.9 ± 1.9 Placebo: 16 ± 1.7	Randomized, placebo controlled trial	Maximum of 1000 mg/day for those weighing <50 kg, 1500 mg/day for those weighing 50–75 kg, or 2000 mg/day for those weighing >75 kg.	The placebo appeared identical to the metformin tablets.	12	BMI Change: −0.05 ± 1.0	BMI Change: 0.2 ± 0.5	No	Twenty-seven adolescents with type 1 diabetes aged 12–17 years	Fasting glucose
17. Anagnostou et al. (2016)[18]	F: 15 M: 45 Both: 60 Metformin: 28 Placebo: 32	Metformin: 12.9 ± 2.85 Placebo: 12.7 ± 2.64	Randomized clinical trial	Metformin or matching placebo titrated up to 500 mg twice daily for children aged 6–9 years and 850 mg twice daily for those 10–17 years.	The placebo appeared identical to the metformin tablets.	16	BMI Change: −0.43 (−0.80 to −0.06) Weight: Change: 0.07 (−0.88 to 1.02)	BMI: Change: 0.52 (0.18–0.87) Weight: Change: 2.80 (1.90–3.70)	No	Sixty children and adolescents with autism spectrum disorder	No
18. Freemark and Bursey (2001)[10]	F: 18 M: 11 Both: 29 Metformin: 14 placebo: 15	Metformin: 14.4 ± 0.6 Placebo: 15.4 ± 0.5	Randomized, double-blind, placebo-controlled trial	Patients received metformin 500 mg twice daily.	Patients received placebo 500 mg twice daily.	24	BMI: Change: −0.50 ± 0.12	BMI: Change: 0.90 ± 0.23	No	Twenty-nine white and black adolescents aged 12–19 years. All had BMIs exceeding 30 kg/m^2.	No
19. El-Sharkawy et al. (2014)[25]	F: 60 Metformin: 30 Control: 30	Metformin: 16.2 ± 0.7 Control: 15.9 ± 0.36	Randomized clinical trial	Patients who were randomly assigned to receive metformin tablets in a dose of 850 mg twice daily orally for 3 months.	Untreated PCOS patients.	12	Before int: BMI: 34.23 ± 0.51 After int: BMI: 26.18 ± 0.43 Before int: Weight: 75.89 ± 1.45 After int: Weight: 57.21 ± 1.1	Before int: BMI: 35.25 ± 0.73 After int: BMI: 36.28 ± 0.81 Before int: Weight: 78.81 ± 2.13 After int: Weight: 77.8 ± 1.55	No	Ninety adolescent girls with PCOS, aging from 12 to 18 years.	No

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Table 1. General Characteristics of Included Studies *continued*

Code/Author (year)	Subjects and gender	Age range, years Mean	RCT	Intervention type		Duration, weeks	Outcome, kg		Any other intervention (from)	Notes about subjects	Adjustment
				Intervention (name and composition)	Control (name and composition)		Intervention, mean ± SD Number	Control, mean ± SD Number			
20. Nwosu et al. (2015)[43]	F: 15 M: 13 Both: 29 Metformin: 15 placebo: 13	Metformin: 15.0±2.5 Placebo: 14.5±3.1	A randomized, double-blind, placebo controlled trial	Metformin arm consisting of treatment with adjunctive metformin at a dose of 1000 mg daily for 9 months.	Control arm consisting of treatment with similar-appearing placebo capsules daily for 9 months.	38	Before int: BMI: 28±5.8 After int: BMI: 28.6±5.1 Before int: Weight: 70.5±18.7 After int: Weight: 74.2±16.8 Before int: WC: 94.6±22 After int: WC: 97.7±25.2	Before int: BMI: 27.7±4.1 After int: BMI: 28.8±3.1 Before int: Weight: 73±18.3 After int: Weight: 77.3±15.6 Before int: WC: 92.1±13.1 After int: WC: 94.6±10.2	No	Twenty-nine overweight/obese youth with T1D, aging from 10 to 20 years.	Baseline values
21. Klein et al. (2006)[35]	F: 17 M: 21 Both: 38 Metformin: 18 Placebo: 20	Metformin: 12.9±2.4 Placebo: 13.3±2.4	A randomized, double-blind, placebo-controlled trial	Subjects were given 850 mg twice a day.	Capsule containing an identical appearing placebo.	16	BMI Change: −0.43±1.07 Weight Change: −0.13±2.88 WC: Change: −2.51±5.46	BMI Change: 1.12±2.02 Weight Change: 4.01±6.23 WC: Change: 3.64±6.91	No	Children ages 10–17, treated with a targeted atypical antipsychotic agent olanzapine, risperidone, or quetiapine	Race, sex, or baseline measure
22. Luong et al. (2015)[39]	Metformin: 28 Control: 56	Total: 13.0±2.5	A randomized clinical trial	Metformin dose varied from 750 mg twice a day to 1000 mg twice a day depending on the prescriber.	Control group with nonmetformin treated group.	52	Before int: BMI: 37.4±7.8 After int: BMI: 36.9±8.8 Before int: Weight: 98.3±32.2 After int: Weight: 98.2±33.4	Before int: BMI: 41.3±8.3 After int: BMI: 41.3±8.3 Before int: Weight: 110.3±29.7 After int: Weight: 111.4±29.0	No	Children with metabolic syndrome, aged 8–18 years.	No
23. Rynders et al. (2012)	F: 9 M: 7 Both: 16 Metformin: 7 Control: 9	Metformin: 15.0±2.0 Control: 13.4±1.7	A randomized clinical trial	Diet and exercise plus metformin.	Diet and exercise alone.	24	Before int: BMI: 33.6±7.2 After int: BMI: 30.9±6.5 Before int: Weight: 90.2±21.8 After int: Weight: 85.1±20.1 Before int: Fat mass: 37.7%±7.4% After int: Fat mass: 33.3%±8.7%	Before int: BMI: 33.6±3.4 After int: BMI: 32.6±2.6 Before int: Weight: 93.9±13.8 After int: Weight: 90.9±12.9 Before int: Fat mass: 39.5%±4.1% After int: Fat mass: 37.0%±3.2%	Diet and exercise	Sixteen obese pubertal adolescents between the ages of 10 and 17.	No
24. Mauras et al. (2012)[40]	F: 36 M: 30 Both: 66 Metformin: 35 Control:31	Metformin: 12.3±0.5 Control: 12.0±0.4	A randomized clinical trial	Diet and exercise plus metformin.	Diet and exercise alone.	24	BMI Change: −2.4±0.5 Weight Change: −4.9±1.0 WC: Change: −6.7±1.8 Fat mass: Change: −3.9±0.7	BMI Change: −1.1±0.5 Weight Change: −1.7±1.1 WC: Change: v0.3±2.1 Fat mass: Change: −2.0±0.8	Diet and exercise	Sixty-six obese children with normal glucose tolerance but elevated highly sensitive C reactive protein	Gender and/or puberty

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Table 1. General Characteristics of Included Studies *continued*

Code/Author (year)	Subjects and gender	Age range, years Mean	RCT	Intervention type		Duration, weeks	Outcome, kg		Any other intervention (from)	Notes about subjects	Adjustment
				Intervention (name and composition)	Control (name and composition)		Intervention, mean ± SD Number	Control, mean ± SD Number			
25. Pastor-Villaescusa et al. Prepubertal (Tanner Stage I 2017)[45]	Metformin: 73 Placebo:74	7–14	Randomized, prospective, double-blind, placebo-controlled trial	500 mg metformin twice daily.	The placebo appeared identical to the metformin tablets.	24	Before int: BMI: 28.2 ± 0.6 After int: BMI: 26.5 ± 0.7 Before int: Weight: 55.8 ± 2.1 After int: Weight: 54.0 ± 2.2 Before int: WC: 89.3 ± 2.0 After int: WC: 88.7 ± 2.0 Before int: Fat mass: 37 ± 0.8 After int: Fat mass: 35 ± 1.0	Before int: BMI: 29.2 ± 0.6 After int: BMI: 28.2 ± 0.6 Before int: Weight: 59.9 ± 2.0 After int: Weight: 60.2 ± 2.2 Before int: WC: 94.5 ± 1.9 After int: WC: 94.6 ± 1.9 Before int: Fat mass: 38 ± 0.8 After int: Fat mass: 37 ± 1.0	No	Eighty prepubertal and 80 pubertal nondiabetic children who were obese aged 7–14 years with a BMI >95th percentiles were recruited.	Baseline values
26. Pastor-Villaescusa et al. Prepubertal (Tanner Stages II–V 2017)[45]	Metformin: 75 Placebo:78	7–14	Randomized, prospective, double-blind, placebo-controlled trial	500 mg metformin twice daily.	The placebo appeared identical to the metformin tablets.	24	Before int: BMI: 29.4 ± 0.5 After int: BMI: 28.5 ± 0.6 Before int: Weight: 76.9 ± 2.4 After int: Weight: 77.4 ± 2.5 Before int: WC: 93.7 ± 1.8 After int: WC: 92.9 ± 1.9 Before int: Fat mass: 38 ± 0.9 After int: Fat mass: 37 ± 1.0	Before int: BMI: 30.6 ± 0.5 After int: BMI: 30.2 ± 0.5 Before int: Weight: 80.5 ± 2.4 After int: Weight: 81.7 ± 2.4 Before int: WC: 95.4 ± 1.8 After int: WC: 94.6 ± 1.9 Before int: Fat mass: 37 ± 0.8 After int: Fat mass: 37 ± 1.0	No	Eighty prepubertal and 80 pubertal nondiabetic children who were obese aged 7 to 14 years with a BMI >95th percentiles were recruited.	Baseline values
27. Sarnblad et al. (2003)[12]	F:18 M: 8 Both: 26 Metformin: 13 Placebo: 13	Metformin: 17.2 ± 1.7 Placebo: 16.9 ± 1.4	Randomized, Double-blind, Placebo-Controlled Trial	The initial study dose was 500 mg daily in the morning for 1 week, and this was followed by 500 mg twice daily for 3 weeks, and subsequently 1000 mg twice daily for the rest of the study period.	Placebo	12	Before int: BMI: 25.2 ± 4.2 After int: BMI: 24.8 ± 4 Before int: Weight: 69.5 ± 8.5 After int: Weight: 69.7 ± 7.2 Before int: WC: 84.2 ± 11.6 After int: WC: 81.6 ± 7.2	Before int: BMI: 23.5 ± 3.05 After int: BMI: 23.4 ± 2.92 Before int: Weight: 68.1 ± 9.1 After int: Weight: 69.2 ± 8.5 Before int: WC: 82.3 ± 8.6 After int: WC: 83.3 ± 9.4	No	Adolescents with type 1 diabetes.	No
28. Burgert et al. (2008)[22]	F: 19 M: 9 Both: 28 Metformin: 15 Placebo: 13	Metformin: 15 ± 2 Placebo: 15 ± 1	Randomized, double-blind, placebo-controlled trial	One pill (500 mg) in the morning and two pills in the evening.	Control group takes one pill in the morning and two pills in the evening.	16	BMI Change: −0.9 ± 0.58 Weight Change: −1.3 ± 1.88	BMI Change: 1.1 ± 0.63 Weight Change: 2.6 ± 2.01	No	The subjects had to be healthy, have Tanner stage 3–5 pubertal development, be 13–18 years, and have a fasting insulin level upper 30 mU/L and a fasting plasma glucose lower 100 mg/dL at a recent screening clinic visit.	Baseline values
29. van der Aa et al. (2016)	F: 28 M: 14 Both: 42 Metformin: 23 Placebo: 19	Metformin: 13.6 ± 2.5 Placebo: 12 ± 1.3	Randomized, double-blind, placebo-controlled trial	Two tablets (500 mg) twice daily in the fourth study week. Subjects were advised to take the medication during or after breakfast and dinner.	Placebo	77	BMI Change: 0.2 ± 1.07 Weight Change: 1.6 ± 2.57 Fat mass Change: −3.1 ± 1.3	BMI Change: 1.2 ± 0.68 Weight Change: 12 ± 3.64 Fat mass Change: −0.8 ± 1.22	No	Adolescents with obesity aged 10–16 years old with insulin resistance.	No

continued on page 9

Table 1. General Characteristics of Included Studies *continued*

Code/Author (year)	Subjects and gender	Age range, years Mean	RCT	Intervention type		Duration, weeks	Outcome, kg		Any other intervention (from)	Notes about subjects	Adjustment
				Intervention (name and composition)	Control (name and composition)		Intervention, mean ± SD Number	Control, mean ± SD Number			
30. Gómez-Díaz et al. (2012)[28]	F: 29 M: 23 Both: 52 Metformin: 28 Placebo: 24	Metformin: 11.9±2.4 Placebo: 12±3	Randomized, double-blind, placebo-controlled trial	850 mg of metformin twice daily for 12 weeks.	Placebo	12	Before int: BMI: 31.1±6.3 After int: BMI: 26.8±7.38 Before int: Weight: 73.5±22.3 After int: Weight: 64.4±23.03 Before int: WC: 100±16.5 After int: WC: 90.7±16.5	Before int: BMI: 27.1±5.9 After int: BMI: 26.1±4.74 Before int: Weight: 62.8±23.7 After int: Weight: 62.1±16.8 Before int: WC: 9.7±17 After int: WC: 85±13	No	Patients aged 4–17 years with glucose intolerance.	No
31. Wiegand et al. (2010)[49]	Both: 63 Metformin: 34 Placebo: 29	Metformin: 13.7±2.1 Placebo: 12.8±3.1	Randomized, double-blind, placebo-controlled trial	500 mg twice/day metformin.	Placebo	18	Before int: BMI: 34.2±4.9 After int: BMI: 34.3±5.2	Before int: BMI: 35.4±5.7 After int: BMI: 35.1±5.1	No	Obese adolescents at risk of developing type 2 diabetes according to American Diabetes Association criteria.	No
32. Clarson et al. (2009)[24]	Both: 25 Metformin: 11 Control: 14	10–16	Randomized, controlled trial	Subjects receiving metformin started therapy at 500 mg/day, increasing by 500 mg/day every 7 days to a maximum tolerated dose of 500 mg×3 per day+ Lifestyle.	Lifestyle alone	18	BMI Change: −1.8±2.6	BMI Change: 0.5±1.1	No	Obese subjects aged 10–16 years, defined as BMI greater than the 95th percentile for age and gender and who were also insulin resistant.	No
33. Bridger et al. (2006)[21]	Both: 21 Metformin: 11 Placebo: 10	Metformin: 16±0.97 Placebo: 16±1.3	Randomized, double-blind, placebo-controlled trial	750 mg of metformin	Placebo	12	BMI Change: −0.16±0.33	BMI Change: −0.19±0.33	No	Adolescents With PCOS.	No
34. Garibay-Nieto et al. (2016)[27]	Metformin: 14 Placebo:17	Metformin: 11.43±2.1 Placebo: 12.59±2.62	A randomized, double-blind, placebo controlled trial	3000 mg metformin daily.	The placebo appeared identical to the metformin tablets.	16	Before int: BMI: 28.5±2.8 After int: BMI: 26.1±0.9 Before int: Weight: 63.2±12.6 After int: Weight: 60.9±3.4 Before int: WC: 87.1±7.6 After int: WC: 82.3±1.9	Before int: BMI: 28.8±2.8 After int: BMI: 27.5±0.8 Before int: Weight: 70.1±13.1 After int: Weight: 66.5±3.2 Before int: WC: 89.4±8.4 After int: WC: 84.9±1.8	No	Patients with obesity aged 8–18 years who had not been previously intervened and had optimal psychological health were included in the study.	No
35. Adeyemo et al. (2015)[17]	F: 33 M: 51 Both: 84 Metformin: 45 Placebo: 39	Metformin: 10.1±0.25 Placebo: 10.3±0.22	A randomized, double-blind, placebo controlled trial	Starting at 500 mg twice daily, the study medication dose was increased over a 3-week period to a maximum of 1000 mg twice daily, based on tolerability.	The placebo appeared identical to the metformin tablets	24	BMI Change: −0.78±0.3 Weight Change: 1.47±1.4 Fat mass Change: 0.48±0.7 Lean Body mass Change: 1.19±0.36	BMI Change: 0.32±0.3 Weight Change: 4.85±0.5 Fat mass Change: 1.88±0.9 Lean Body mass Change: 3.44±0.45	No	Obese, insulin-resistant, but otherwise healthy children, between the ages of 6 and 12 years, were recruited.	Baseline values

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Table 1. General Characteristics of Included Studies *continued*

Code/Author (year)	Subjects and gender	Age range, years Mean	RCT	Intervention type		Duration, weeks	Outcome, kg		Any other intervention (from)	Notes about subjects	Adjustment
				Intervention (name and composition)	Control (name and composition)		Intervention, mean ± SD Number	Control, mean ± SD Number			
36. Díaz et al. (2015)[25]	F: 13 M: 10 Both: 23 Metformin: 6 Placebo: 17	Metformin: 7.8±0.4 Placebo: 7.7±0.3	Double-blind, placebo-controlled, pilot study	425 mg metformin daily.	The placebo appeared identical to the metformin tablets	96	BMI Change: 0.5±0.4 Weight Change: −0.6±0.2 WC Change: 0.9±1 Fat mass Change: 2.4±0.6 Lean Body mass Change: 4.5±0.5	BMI Change: 2.3±0.4 Weight Change: 0±0.1 WC Change: 5.3±1.8 Fat mass Change: 5.2±0.8 Lean Body mass Change: 5.4±0.2	No	Post-catch-up nonobese prepubertal small for gestational age (SGA) children [age, 7.7 years; BMI SD score (BMI SDS) >50th and <97th centile for age].	No
37. Yanovski et al. (2011)[51]	F: 60 M: 40 Both: 84 Metformin: 53 Placebo: 47	Metformin: 10.1±1.6 Placebo: 10.4±1.4	A randomized clinical trial	1000 mg metformin twice daily.	The placebo appeared identical to the metformin tablets.	24	BMI Change: −0.78±0.4 Weight Change: 1.47±0.9 WC Change: 1.84±1.45 Fat mass Change: 0.48±0.65	BMI Change: 0.32±0.43 Weight Change: 4.85±0.95 WC Change: 4.38±1.6 Fat mass Change: 1.88±0.73	No	Obese children, aged 6–12 years, were eligible if they had BMI ≥95th percentile according to the Centers for Disease Control and Prevention 2000 growth charts for the United States.	Age, race, and sex
38. Casteels et al. (2009)[23]	F: 23 M: 19 Both: 42 Metformin: 19 Placebo: 23	Metformin: 16±6 Placebo: 15±6	A randomized clinical trial	425 mg/day (age <10 years) or 850 mg/day (age ≥10 years).	The placebo appeared identical to the metformin tablets.	24	BMI Change: −0.28±0.22 Weight Change: 0.32±0.44 Fat mass Change: 0.13±0.29	BMI Change: 0.68±0.28 Weight Change: 1.92±0.48 Fat mass Change: 0.64±0.35	No	Children with a neurogenic or myogenic motor deficit.	No
39. Ibanez et al. (2008)[31]	F: 38 Metformin: 19 Control: 19	Metformin: 7.9 Control: 7.9	A randomized clinical trial	850 mg metformin daily.	Untreated	192	BMI Change: −0.8±0.2 Weight Change: 19±1 Fat mass Change: 4.8±0.7 Lean Body mass Change: 12.2±0.5	BMI Change: 0.1±0.3 Weight Change: 24±2 Fat mass Change: 10.3±1.2 Lean Body mass Change: 12±0.8	No	The study population consisted of 38 low birth weight (LBW)-Girls, distributed into two well-matched subgroups of 19 girls each.	Baseline values
40. Jones et al. (2002)[32]	F: 57 M:25 Both: 82 Metformin: 42 Placebo: 40	Metformin: 13.9±1.8 Placebo: 13.6±1.8	A randomized controlled trial	1000 mg metformin twice daily.	The placebo appeared identical to the metformin tablets.	16	BMI Change: −0.5±0.16 Weight Change: −1.5±0.5	BMI Change: −0.4±0.13 Weight Change: −0.9±0.3	No	Pediatric patients with type 2 diabetes.	Baseline values

CI, confidence interval; DXA, dual-energy X-ray absorptiometry; Int, intervention; NAFLD, nonalcoholic fatty liver disease; PCOS, polycystic ovary syndrome; RCT, randomized controlled trial; SD, standard deviation; T1DM, type 1 diabetes mellitus; WC, waist circumference.

values of anthropometric measures was conducted in 16 studies.[17,22,29,31–37,40,43–45,50,51] Twenty-two studies did not report any adjustment.[10–11,12,18–21,23–28,30,38,39,41,42,46–49]

Findings from Meta-Analysis

Effects of metformin therapy on BMI. Combining effect sizes from included studies, we found a significant reduction in BMI after metformin therapy in patients with chronic diseases [weighted mean difference (WMD): −1.19 kg/m^2; 95% CI: −1.63 to −0.74], growth problems (WMD: −1.21 kg/m^2; 95% CI: −1.67 to −0.76), and psychological disorders (WMD: −1.11 kg/m^2; 95% CI: −1.94 to −0.27); however, this effect was not significant among those with overweight or obesity (WMD: −0.76 kg/m^2; 95% CI: −1.61 to 0.08) (Fig. 2A). When we combined effect sizes from all studies about BMI, a significant reduction in BMI was found after metformin therapy comparing with control (WMD: −1.07 kg/m^2; 95% CI: −1.43 to −0.72) (Fig. 2B). Due to the high between-study heterogeneity ($I^2 = 98.8\%$), we conducted subgroup analyses based on study design (with and without placebo), participants' age (<10, 10–15, and ≥15 years) and gender (female or both), metformin dosage (<1000, 1000–1500, 1500–2000, and >2000 mg/day), and duration of study (<6 months, 6 months to 1 year, and ≥1 year) (Supplementary Fig. S1). Among that, stratification by participants' age could explain the heterogeneity (for aged 5–10 years: $I^2 = 44.6\%$). In addition, a significant reduction in BMI was seen in all subgroups following metformin therapy, except for studies conducted in females (WMD: −1.88 kg/m^2; 95% CI: −4.73 to 0.97). Sensitivity analysis showed that an individual study had no great influence on the overall results (data did not show). We found publication bias in the included studies ($P_{begg} < 0.001$). Therefore, the trim and fill test was used to correct the bias; however, no further study was recommended by the test.

Effects of metformin therapy on body weight. Pooling effect sizes, a significant reduction in body weight following metformin therapy was found in participants with different health conditions (for overweight or obesity: WMD: −2.06 kg; 95% CI: −3.47 to −0.65; for chronic disease: WMD: −3.09 kg; 95% CI: −4.13 to −2.05; for growth problems: WMD: −1.30 kg; 95% CI: −2.30 to −0.29; and for psychological disorders: WMD: −2.09 kg; 95% CI: −4.07 to −0.12) (Fig. 3A). Pooling analysis of data from all included studies did not change the finding (WMD: −2.51 kg; 95% CI: −3.14 to −1.89); however, between-study heterogeneity was high ($I^2 = 96.6\%$). None of our subgroup analyses could explain the heterogeneity (Fig. 3B). No significant effect of metformin was found in studies conducted in children aged 5–10 years old (WMD: −2.24 kg; 95% CI: −6.44 to 1.93), studies did not use placebo (WMD: 1.53 kg; 95% CI: −7.25 to 10.31), those used metformin in dosages of 1500–2000 mg/day (WMD: −0.64 kg; 95% CI: −5.99 to 4.70), or conducted in females (WMD: −11.47 kg; 95% CI: −23.89 to 0.94), and studies with a duration of ≥1 year (WMD: 1.28 kg; 95% CI: −1.95 to 4.50). Metformin therapy in all other subgroups caused significant reduction in body weight (Supplementary Fig. S2). No evidence for publication bias ($P_{begg} = 0.77$) and for a great influence of an individual study on overall findings was found in this regard.

Effects of metformin therapy on WC. After pooling effect sizes, we found a significant reduction in WC after administration with metformin in patients who had chronic diseases (WMD: −1.83 cm; 95% CI: −2.57 to −1.08), growth problems (WMD: −6.45 cm; 95% CI: −9.83 to −3.07), and psychological disorders (WMD: −6.15 cm; 95% CI: −10.61 to −1.69). However, no significant effect of metformin was found in patients with overweight or obesity (WMD: −0.64 cm; 95% CI: −1.78 to 0.49) (Fig. 4A). When we combined effect sizes of all included studies, we found a significant reduction in WC following intake of metformin (WMD: −1.93 cm; 95% CI: −2.69 to −1.16), with high between heterogeneity ($I^2 = 91.4\%$) (Fig. 4B). Subgroup analysis based on participants' age (5–10 years: $I^2 = 48.2\%$ and ≥15 years: $I^2 = 46.9\%$), metformin dosage (500–1000 mg/day: $I^2 = 48.2\%$ and 1000–1500 mg/day: $I^2 = 30.6\%$), and trial duration (<6 months: $I^2 = 36.5\%$) explained the heterogeneity. Significant reduction in WC following metformin therapy was seen in all subgroup analyses, except for studies conducted among females (WMD: −2.84 cm; 95% CI: −8.46 to 2.78), and those used metformin in dosages of 1500 – 2000 mg/day (WMD: −2.70 cm; 95% CI: −5.55 to 0.15) (Supplementary Fig. S3). We found no evidence for publication bias ($P_{begg} = 0.06$) and for a great influence of an individual study on the overall results.

Effects of metformin therapy on body fat mass. Combining effect sizes, a significant reduction in body fat mass following metformin administration was found in studies conducted in patients with overweight or obesity (WMD: −1.90%; 95% CI: −3.25 to −0.56) and chronic diseases (WMD: −1.41%; 95% CI: −2.23 to −0.58), but not among those with growth problems (WMD: −2.68%; 95% CI: −5.50 to 0.13) (Fig. 5A). Pooling data from all studies revealed a significant reduction in body fat mass following intake of metformin rather than control (WMD: −1.65%; 95% CI: −2.27 to −1.03; $I^2 = 95.1\%$) (Fig. 5B). Stratification by the metformin dosage (1500–2000 mg/day: $I^2 = 0\%$) explained the heterogeneity. Moreover, reduction of body fat mass following metformin therapy was significant in all subgroup analyses, except for studies that used metformin in dosages of <1000 mg/day (WMD: −2.68%; 95% CI: −5.55 to 0.13) (Supplementary Fig. S4). We found no evidence of publication bias ($P_{begg} = 0.24$), and sensitivity analysis that revealed no specific study had a significant influence on the overall results.

Effects of metformin therapy on LBM. Combining effect sizes of included studies, we failed to find a significant effect of metformin therapy on LBM in patients with

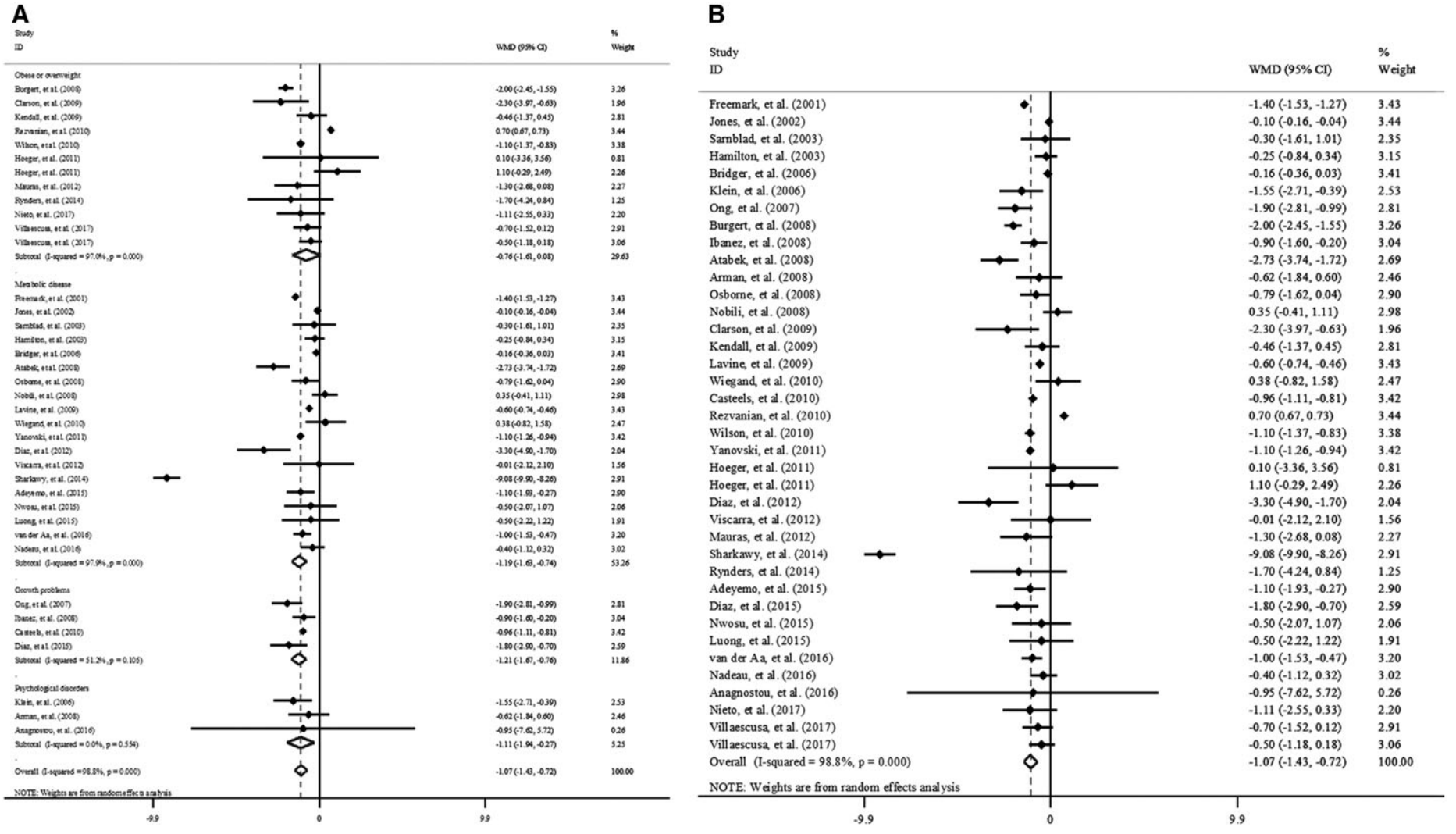

Figure 2. **Forest plot for the effect of metformin on BMI (kg/m^2) separately by the participants' health condition (A) and among all participants (B), expressed as the mean differences between the intervention and the control groups. The area of each square is proportional to the inverse of the variance of the WMD. Horizontal lines represent 95% CIs. Diamonds represent pooled estimates from the random-effects analysis. CI, confidence interval; WMD, weighted mean difference.**

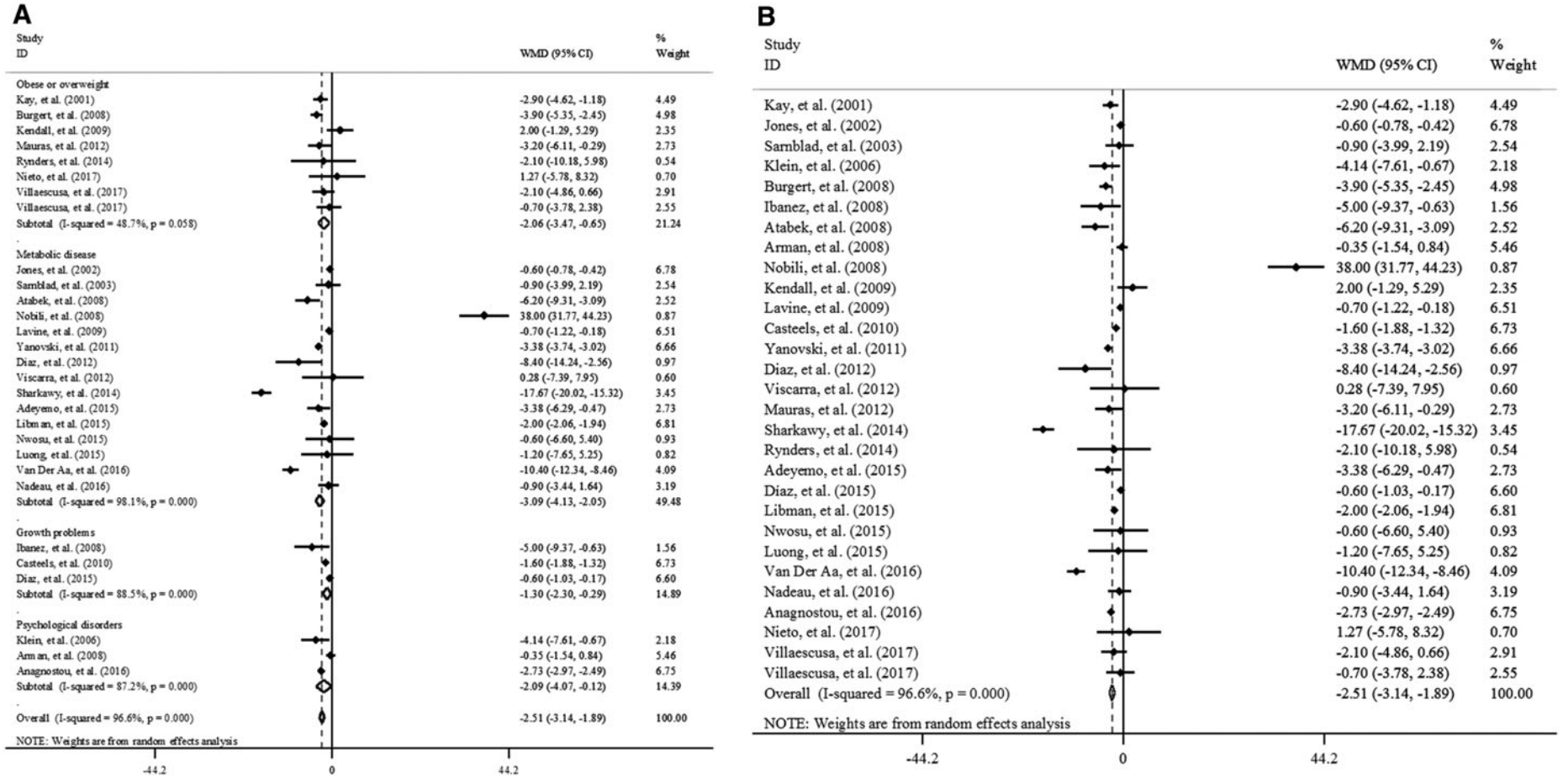

Figure 3. Forest plot for the effect of metformin on body weight (kg) separately by the participants' health condition (A) and among all participants (B), expressed as the mean differences between the intervention and the control groups. The area of each square is proportional to the inverse of the variance of the WMD. Horizontal lines represent 95% CIs. Diamonds represent pooled estimates from the random-effects analysis.

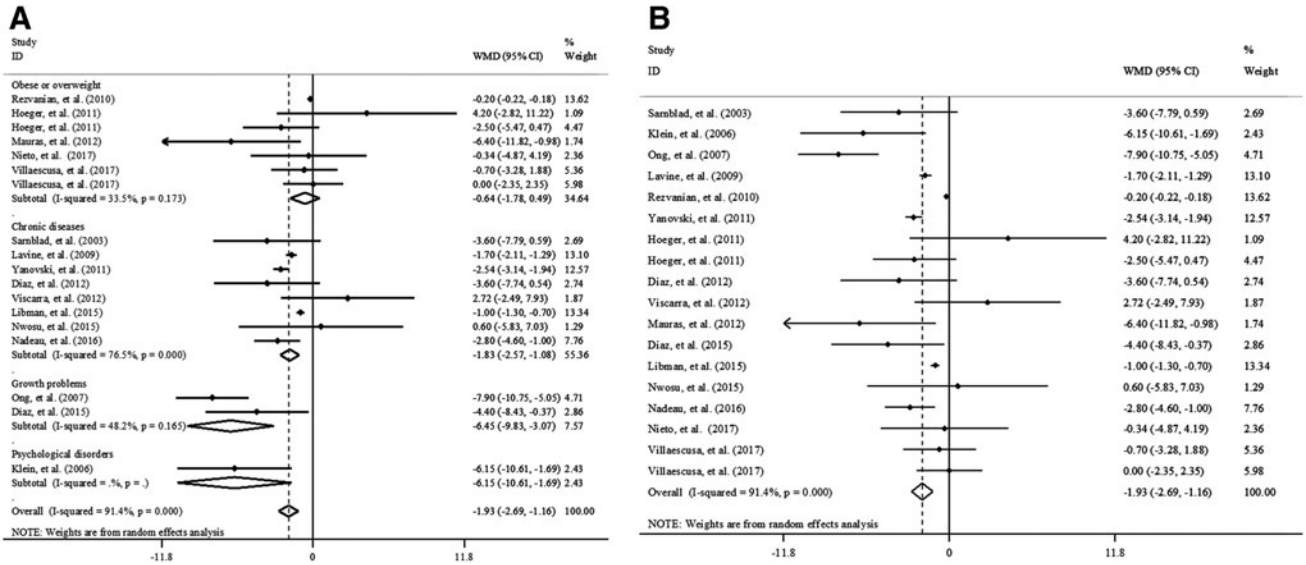

Figure 4. Forest plot for the effect of metformin on waist circumference (cm), separately by the participants' health condition (A) and among all participants (B), expressed as the mean differences between the intervention and the control groups. The area of each square is proportional to the inverse of the variance of the WMD. Horizontal lines represent 95% CIs. Diamonds represent pooled estimates from the random-effects analysis.

overweight or obesity (WMD: −0.74 kg; 95% CI: −2.40 to 0.91) and those with growth problems (WMD: 0.69 kg; 95% CI: −1.71 to 3.09). However, a significant reduction was found in LBM after metformin therapy in two studies conducted among patients with chronic diseases (WMD: −1.49 kg; 95% CI: −2.69 to −0.30) (Fig. 6A). The effect of metformin on LBM was also nonsignificant in the combined analysis of data from all studies (WMD: −0.51 kg; 95% CI: −1.29 to 0.27; $I^2 = 81.6\%$) (Fig. 6B). Our subgroup analysis could not explain the between-study heterogeneity. Although a significant reduction in LBM after metformin administration was found in studies with a duration of <1 year (WMD: −1.04 kg; 95% CI: −2.04 to −0.05), studies used ≥1000 mg/day metformin (WMD: −1.18 kg; 95% CI: −1.79 to −0.57), and those conducted in children with ≥10 years old (WMD: −1.18 kg; 95% CI: −1.79 to −0.57), the effect was nonsignificant among other subgroups (Supplementary Fig. S5). We found neither publication bias ($P_{begg} = 0.23$) nor great influence of an individual study on our findings in this regard.

Discussion

This study showed a significant reduction in BMI, body weight, WC, and fat mass, but not in LBM following intake of metformin. However, changes in BMI and WC were not

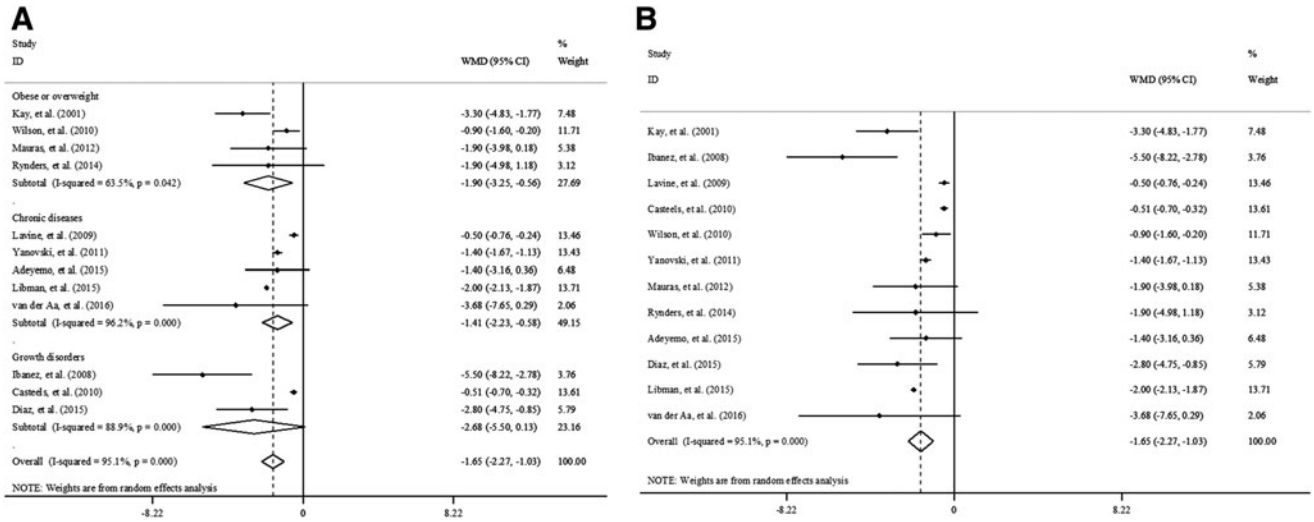

Figure 5. Forest plot for the effect of metformin on body fat mass (%), separately by the participants' health condition (A) and among all participants (B), expressed as the mean differences between the intervention and the control groups. The area of each square is proportional to the inverse of the variance of the WMD. Horizontal lines represent 95% CIs. Diamonds represent pooled estimates from the random-effects analysis.

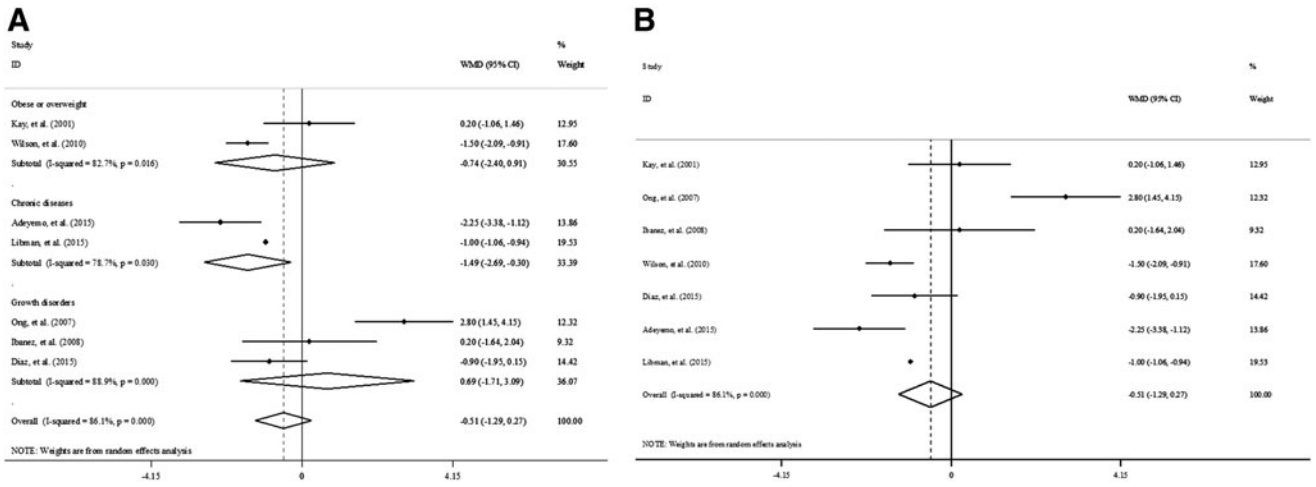

Figure 6. Forest plot for the effect of metformin on lean body mass (kg), separately by the participants' health condition (A) and among all participants (B), expressed as the mean differences between the intervention and the control groups. The area of each square is proportional to the inverse of the variance of the WMD. Horizontal lines represent 95% CIs. Diamonds represent pooled estimates from the random-effects analysis.

significant among participants who were overweight or obese. The effect was also nonsignificant for fat mass in patients with growth problems and LBM in patients with chronic diseases, among only two studies conducted in these subgroups.

We found a significant reduction in BMI after metformin therapy. A systematic review in children aged 18 years or younger showed a statistically significant decrease in BMI following metformin therapy when combined with lifestyle interventions.[52] Metformin also modulated weight gain induced by olanzapine, as found in another systematic review.[53] However, the effect of metformin on BMI was nonsignificant in some studies.[39,49] In addition, our subgroup analysis also showed that the effect of metformin therapy on BMI was not significant among females and patients with overweight or obesity. As a higher percentage of body weight in females compared to males has consisted of fat,[54] it seems that higher doses of metformin is required to influence BMI in subjects with higher body fat.

Metformin therapy in our meta-analysis caused a significant reduction in body weight. A narrative review in 2014 showed that metformin induces modest weight loss in overweight and obese individuals at risk for diabetes.[55] Moreover, two other systematic reviews have also concluded similar findings.[52,53] Otherwise, some studies failed to find a significant effect of metformin on participants' body weight.[11,12] It should be noted that the duration and dosage of metformin therapy in most of these studies were lower than other studies in this area. Subgroup analysis in our meta-analysis revealed that intake of metformin in higher dosages for up to 1 year caused more reduction in patients' body weight. We failed to find a significant effect of metformin on body weight among studies conducted in females and children aged 5–10 years; however, only two studies were included in each of these subgroups.

Metformin therapy also reduced WC in our study. A systematic review in this regard found that metformin reduced WC by a higher amount than orlistat at 6 months.[56] Metformin also reduced WC in patients who suffered from psychological medicine-induced obesity.[53,57] However, some other studies did not find such an effect.[11,43] In addition, the result was also nonsignificant among studies that were conducted in females and subjects with overweight and obesity. As mentioned for BMI, it seems that the effect of metformin on the modulation of obesity in subjects with higher accumulation of fat is low. Strangely, the impact of metformin on WC was also nonsignificant in dosages of 1500–2000 mg/day, despite other doses. However, the effect was near the significance.

Metformin therapy also reduced body fat mass in the current study. It is in line with findings from several studies in this regard.[55] Although this effect was not significant in studies conducted among those with growth problems and studies used metformin in dosages of <1000 mg/day, the number of studies in these subgroups was low. Furthermore, our meta-analysis on data from rarely available studies showed that metformin did not affect LBM in children and adolescents.

Although exact mechanisms through which metformin might influence obesity indices have not been understood, some suggestions have been made. Intake of metformin might reduce appetite by acting on the central nervous system.[55] Metformin attenuates hypothalamic AMP-activated protein kinase activity, which subsequently reduces neuropeptide Y (orexigenic) and increases proopiomelanocortin (anorectic) expression.[58] Metformin therapy also improves leptin and insulin sensitivity and through which might affect food intake.[59] In addition, it has been suggested that intake of metformin increases fat oxidation, decreases lipid synthesis, and avoids an ectopic fat accumulation.[57] Modulation of gut microbiota and secretion of glucagon like peptide-1 by metformin might also influence food intake and fat accumulation.[60]

This study is the first meta-analysis on the effect of metformin on various obesity indices among children and adolescents. Sensitivity analysis showed that no individual study had influence on our findings. Moreover, we found no evidence of the presence of publication bias among the included studies. However, some limitations of the current study should be taken into account. Variations in intervention period and medication dosage, as well as differences in control groups, are some possible sources of bias in this meta-analysis. In addition, participants in included studies had different physiological conditions. We tried to take into account these variations using subgroup analyses. Furthermore, adjustment for the potential confounders was not performed in most of the included studies. Besides, most of those studies did not completely explain methods used for the measurement of obesity indices.

Conclusions

In conclusion, we found a significant reduction in BMI, body weight, WC, and fat mass following intake of metformin. However, no significant effect of metformin therapy on LBM was found in the current meta-analysis. Further studies, in particular among participants with specific health conditions, are needed to confirm these findings.

Authors' Contributions

A.S. and A.M. conceived and designed the study. A.S., S.M.M., and M.P. conducted the systematic search, screened articles, selected eligible articles, and extracted information from eligible studies. A.M. and T.M. performed analysis and interpreted results. All authors contributed to writing, reviewing, or revising the article. All authors have read, approved the final article, and agreed to submit it to the obesity review.

Funding Information

No funding was received for this article.

Author Disclosure Statement

No competing financial interests exist.

Supplementary Material

Supplementary Figure S1
Supplementary Figure S2
Supplementary Figure S3
Supplementary Figure S4
Supplementary Figure S5

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