Systematic Review and Meta-Analysis

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The effects of metformin on insulin resistance in overweight or obese children and adolescents: A PRISMA-compliant systematic review and meta-analysis of randomized controlled trials

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Abstract

Background: Metformin has shown its effectiveness in reducing body mass index (BMI) in obese children and adolescents, but relevant evidence for improving insulin resistance in overweight or obese children and adolescents is inconclusive.

Objectives: This study aimed to assess whether metformin could effectively and safely improve homeostasis model assessment insulin resistance index (HOMA-IR) and other related laboratory indicators including fasting glucose, fasting insulin, high-density lipoprotein cholesterol (HDL-C), and low density lipoprotein-cholesterol (LDL-C).

Methods: Searches were carried out in PubMed, CENTRAL, Web of Science, EMBASE, CBM, Chinese National Knowledge Infrastructure (CNKI), and WanFang from their inception until March 2018. Randomized controlled trials (RCTs) comparing metformin alone with placebo in overweight or obese children and adolescents were included. The Cochrane risk of bias tool was applied to assess the methodological quality of every study and Meta-analysis was carried out with a random effects model or a fixed effects model. Publication bias was evaluated by the Begg and Egger tests.

Results: A total of 11 trials with a total of 865 participants met the inclusion criteria. Participants were between 4 and 18 years old. The time span of these studies ranged from 2001 to 2017. The daily dose of metformin was from 1000 mg to 2000 mg and the duration of intervention was 8 weeks to 18 months. Compared with placebo, metformin with lifestyle intervention reduced the level of LDL-C ($P = 008$, MD = - 4.29, 95% confidence interval [CI]: -7.45, -1.12). However, there was no obvious differences in improving insulin resistance, fasting glucose, and HDL-C.

Conclusion: Metformin may improve the level of LDL-C, but it has no significant effect on insulin resistance. The use of metformin may be a new approach to lipid metabolism management in overweight or obese children and adolescents.

Registration number: CRD42018092059.

Abbreviations: ALR = adiponectin–leptin ratio, ALT = alanine aminotransferase, BMI = body mass index, BMI-SDS = body mass index standard deviation score, CIs = confidence intervals, CLA = conjugated linoleic acid, FPG = fasting plasma glucose, HbA1c = glycosylated hemoglobin, HDL-C = high-density lipoprotein cholesterol, HOMA-IR = homeostasis model assessment insulin resistance index, IFN-γ = interferon-γ, LDL-C = low density lipoprotein-cholesterol, MD = mean difference, OGTT = oral glucose tolerance test, PAI-1 = plasminogen activator inhibitor-1, QUICKI = quantitative insulin sensitivity check index, RCTs = randomized controlled trials, RR = relative risk, SD = standard deviation, TNF-α = tumor necrosis factor α.

Keywords: adolescents, children, insulin resistance, meta-analysis, metformin, obese, overweight

1. Introduction

Overweight and obesity in children and adolescents are the most serious public health challenges of the 21st century. This problem is global and is steadily affecting many low and middle income countries, particularly in urban settings.[1] The global prevalence of obesity has risen at an alarming rate from 4% in 1975 to 18% in 2016, with an estimated 124 million children and adolescents affected.[2] Obesity plays an important pathophysiological role in insulin resistance, hypertension, and dyslipidemia. Several studies have shown a high correlation between obesity and cardiovascular disease, diabetes and some cancers.[3] This group of people is more likely to develop obesity, premature death and disability in adulthood.

Previous studies have suggested that an intensive lifestyle modification could increase weight loss, improve insulin sensitivity and reduce the risk of developing type 2 diabetes,[4]

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but this single-strategy lifestyle intervention was not always effective.[5] Metformin was an oral antihyperglycemic agent. It was proved to be effective for obesity among children and adolescents who didn't respond to simple lifestyle intervention.[6] Many studies have confirmed that in the short term, metformin combined with standardized lifestyle intervention could reduce body weight and improve insulin sensitivity in obese children and adolescents.

Nevertheless, many investigations have focused on the effects of metformin on weight loss, but lack of attention was paid to the effects of insulin resistance, despite it was one of the outcomes for these studies. Meanwhile, different studies have different views on whether metformin could improve insulin resistance in obese children and adolescents. In such a scenario, the present meta-analysis investigated the efficacy and safety of metformin in improving insulin resistance in overweight or obese children and adolescents, to provide a scientific basis for the application of future clinical evidence.

2. Materials and methods

We registered the current meta-analysis at PROSPERO (CRD42018092059). Ethical approval and patient consent were not required for this study, given that this was a meta-analysis, which utilized published data.

2.1. Data sources and search strategies

A literature search of the electronic databases of PubMed, CENTRAL, Web of science, EMBASE, CBM, Chinese National Knowledge Infrastructure (CNKI), and WanFang was carried out from their inception until March 2018. The MeSH terms were "metformin," "obes*," "overweigh*," "children, " "adolescents". Children in our study were defined as 3 to 12 years old and adolescents were defined as 13 to 18 years old. Overweight was defined as >+1 Standard deviation (SD), BMI > 25 kg/m^2, or BMI > 85th percentile. Obesity was defined as > +2SD, BMI > 30 kg/m^2, or BMI > 95th percentile. The reference lists of full articles were also reviewed. No limitations were placed on the treatment duration and the language of the results report. The detailed search strategy can be seen in Supplemental digital content 1, http://links.lww.com/MD/C775.

2.2. Selection criteria and exclusion criteria

We included the randomized controlled trials that met the following criteria:

1) participants: trials for children and adolescents diagnosed as overweight or obesity;
2) intervention: metformin alone combined with lifestyle changes,;
3) comparison: placebo combined with lifestyle changes;
4) outcomes: at least one objective data of the efficacy and safety variables we need.

Studies were excluded if they were:

1) participants had basic diseases such as diabetes, liver dysfunction, renal insufficiency;
2) metformin combined with other drugs as intervention, lack of lifestyle intervention;
3) no placebo as control;
4) no outcomes for our study.

2.3. Data extraction

Two reviewers (WY and Z XY) independently extracted data from eligible articles with a standard form. Any discrepancies between them were resolved by consensus. Accordingly, the following data and information were included: first author, publication year, country, study design, inclusion criteria, the duration of the intervention, the participant's information included number, age, BMI, the dose and frequency of metformin, drop-out, related outcomes, adverse effects. We would contact the corresponding author if sufficient data of an eligible study could not be obtained from the full text.

2.4. Study quality assessment

The reviewers (WY and Z XY) independently evaluated the methodological quality of the included studies according to the Cochrane risk of bias tool,[7] including 7 domains: randomization sequence generation, allocation concealment, blinding of participants, blinding of study personnel, blinding of outcome assessors, incomplete outcome data, selective reporting, and other sources of bias. For every study, the risk of bias was classified as "high," "low," or "unclear".

2.5. Statistical analysis

Review Manager Version 5.3 software was applied to calculate the 95% confidence intervals (CIs) and the MD for efficacy and safety outcomes. The Stata statistical software version 11.0 software was applied to test the publication bias. Heterogeneity was evaluated using the Cochran Q test and quantified using the I^2 statistic.[8] $I^2 > 50\%$ and $P \leq .05$[9] showed a high heterogeneity and the random-effects model was utilized, otherwise the fixed-effects model should be applied instead. Sensitivity analysis was conducted by using the method of combined data (random or fixed effect models). The subgroup analysis was applied to explore the possible source of heterogeneity. The publication bias was assessed with the Begg and Egger test. All tests were 2 sided and $P < .05$ was considered significant.

3. Results

3.1. Search results

A total of 734 studies were initially searched in this study. Of these, 23 full articles were shortlisted for eligibility assessment. Among the 23 articles, 5 studies were excluded for not meeting the required intervention. In these 5 studies, some of the interventions used were metformin combined with other drugs or different dietary structures, lack of lifestyle intervention, lack of placebo. Six studies were excluded because of non-interested outcomes. The results they provided included BMI, abdominal circumference, height, weight, insulin sensitivity, etc. One study was excluded because we couldn't get the full text. We contacted the corresponding author but did not respond. There were 2 experimental groups in the study of Pastor−villaescusa B, so the study was divided into 2 studies, Pastor−villaescusa B 2017 and 2 Pastor−villaescusa B 2017. Finally, 11 eligible articles were included in this study. The results can be seen in Figure 1.

3.2. Study characteristics and quality assessment

The study characteristics are presented in Table 1. A total of 865 participants between the ages of 4 and 18 were included. The

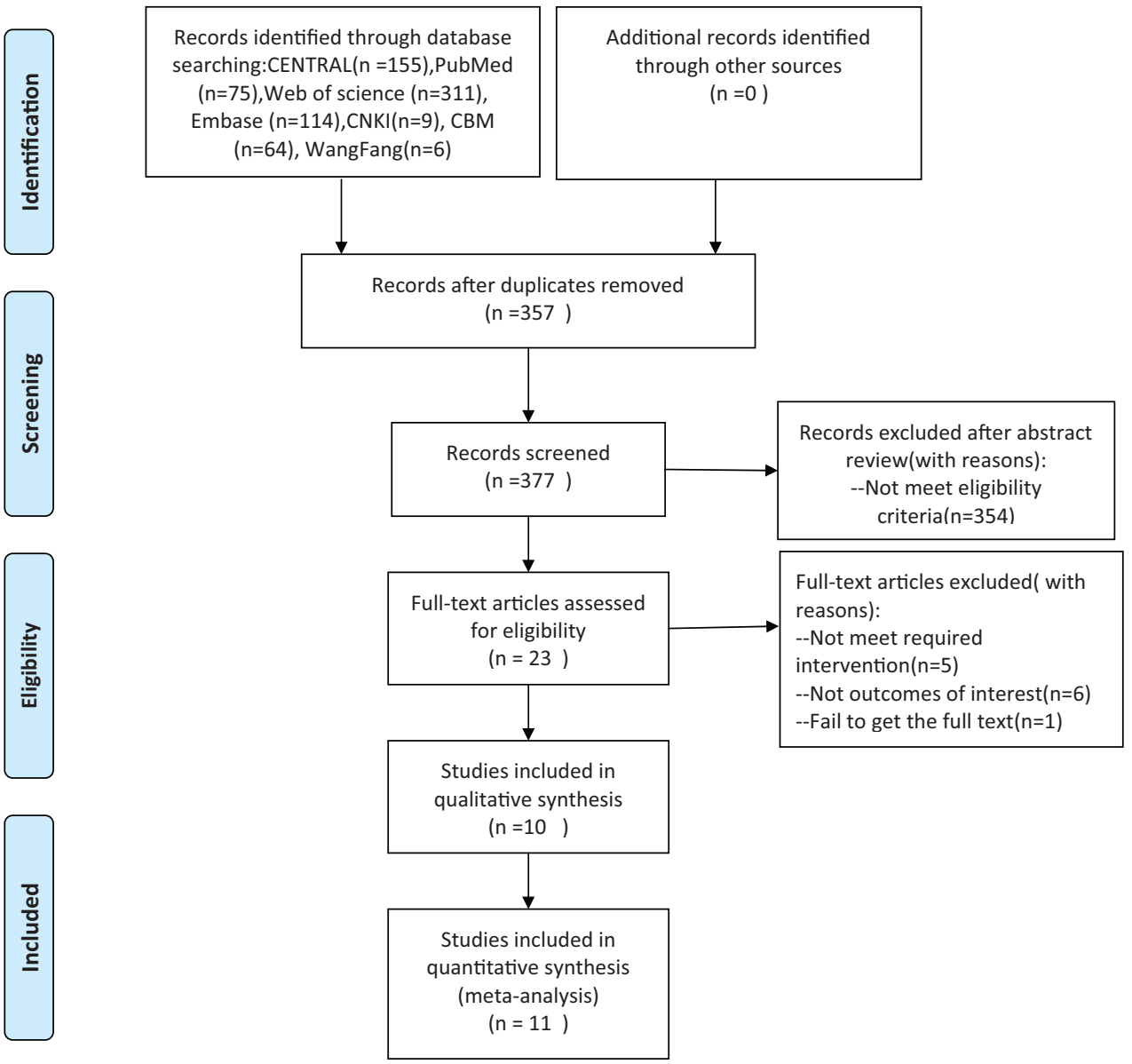

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Figure 1. PRISMA flow diagram.

studies were published in English between 2001 and 2017. The sample sizes ranged from 24 to 160. In addition, the daily doses of metformin ranged from 1000 mg/d to 2000 mg/d and the duration of intervention was 8 weeks to 18 months. Some participants dropped out of studies, mainly due to loss of interest, loss of contact, refusal to participate, etc. The researchers showed no difference in baseline data between the lost and remaining participants. Most studies had shown that metformin was well-tolerated, the treatment compliance was generally good. Researchers monitored the medications through regular visits, counting the remaining tablets and asking if they had forgotten to take the medicine. One of the 11 studies grouped participants according to puberty and prepuberty which showed that metformin was effective for prepubertal participants.

The assessment of bias risk is shown in Figures 2 and 3. Eight of the included studies did not provide a clear description of the detection risks. The performance and reporting risks of the included trials were low. One study was considered to have other sources of bias owing to incomplete data reporting.

3.3. Meta-analysis

3.3.1. HOMA-IR. Nine studies reported changes in HOMA-IR. Figure 4 shows the results. There was no significant heterogeneity among the studies ($P = .20$, $I^2 = 27\%$) and a fixed-effects model was adopted. Compared with placebo, the metformin with lifestyle intervention showed no significant difference in lowering

Table 1

Characteristics of randomized controlled trials included in the meta-analysis.

First author/ Publication year	Country	Design/ Duration	n;Age (y) BMI (initial/final)	Inclusion criteria	Number of cases (initial/ final) Intervention	Number of cases (initial/ final) Comparison	Drop-out Outcomes	Adverse effect
Joan P. kay[10] (2001)	United States	RCT/8 weeks	24/15.±0.4 (M) 15.7±0.5 (P) M:41.2±1.8 (initial) P:40.8±1.4 (initial)	BMI > 30kg/m^2	n=12/12 M:850 mg twice daily Lifestyle intervention	n=12/12 Placebo and lifestyle intervention	M:0; P:0 Significant decrease in weight loss, body fat, and plasma leptin and lipid profiles.	M: Nausea: 5/12; dizziness: 2/12; P: Nausea:0/12 dizziness: 0/12
Mehmet Emre Atabek[11] (2008)	Turkey	RCT/6 months	120/9-17 M:28.5±3.4/26.7±4 P: 28.0±3.4/28.6±4.2	BMI>95th percentile	n=90/90 M:500 mg twice daily Lifestyle intervention	n=30/30 Placebo and lifestyle intervention	M:0; P:0 Significant decline in BMI, fasting insulin and HOMA-IR	Not report
Burgert TS[12] (2008)	United States	RCT/4 months	34/13-18 M:41±6/-0.9±2.5 P:40±6/1.2±1.9	Be healthy, a fasting insulin>30mU/l, a fasting plasma glucose<100mg/dl	n=17/15 M:1500mg/d Lifestyle modification	n=17/13 Placebo and lifestyle modification	M:2; P:4 Significant decrease in BMI	M:1/17 P:1/17
Wilsom DM[13] (2010)	United States	RCT/48 weeks	77/13-18 M:35.9±5.7/35.6±0.8 P:35.9±4.7/36.3±0.9	BMI≧95th percentile But weighed≦136kg	n=39/27 (12months) M:2000mg/d Lifestyle intervention	n=38/27 (12months) Placebo and lifestyle intervention	M:12; P:11 Small but significant decrease in BMI	M: Nausea: 9/39 Headache: 12/39 Vomiting: 6/39 upper respiratory tract infection: 18/39 musculoskeletal complaints: 5/39 P: Nausea: 3/39 Headache: 8/39 Vomiting: 1/39 upper respiratory tract infection: 23/39 musculoskeletal complaints: 7/39
Yanovski[14] (2011)	United States	RCT/6months followed by 6 months open label M	100/6-12 M:34.2±6.8/ 1.47 (-0.31-3.24) P:34.6±6.2/ 4.85 (2.84-6.85)	BMI ≧95th percentile Fasting insulin≧15 μU/ml Without related diseases	n=53/45 (6months) M:1000 mg twice daily Lifestyle modification	n=47/40 (6months) Placebo and lifestyle modification	M:8; P:7 Significant great decrease in BMI, body weight, fat mass Improved fasting plasma glucose, FPG,HOMA-IR	M:1/53 P:1/47
Evia-viscarra[15] (2012)	Mexico	RCT/3 months	31/9-18 M:33.44±5.82/ 32.71±5.77 P:32.82±6.37/ 32.10±6.52	Obese adolescents Tanner stage≧2 With no related diseases	n=15/12 M:500 mg twice daily Lifestyle intervention	n=16/14 Placebo and lifestyle intervention	M:3; P:2 Significant decrease in BMI in both groups, serum fasting insulin and adiponectin decrease in placebo group; serum TNFα decrease in M group	M: 2/15 P: 1/16
D kendall[16] (2012)	United Kingdom	RCT/6 months	151/8-18 M: 37.10±6.35/ 36.85±6.29 P: 35.95±6.32/ 36.16±6.49	BMI>98th percentile 7.8≦0GTT-2h plasma glucose≦11.1mmol/L With or without 6.1≦impaired fasting glucose≦7.0mmol/L Or fasting insulin>26Miu/ L,120-min insulin>89 Miu/ L,(pubertal/postpubertal hildren) fasting insulin>15Miu/L or 120-min insulin>89Miu/L (prepubertal childern	n=74/55 M:1000 mg in the morning and 500 mg in the evening Lifestyle intervention	n=77/55 Placebo and lifestyle intervention	M:19; P:22 Significant reduction in BMI-SDS at 6 months Significant improvement in fasting glucose, ALT, ALR at 3 months.	M: diarrhea, nausea, and abdominal pain: 20/74 P: diarrhea, nausea, and abdominal pain: 8/77

(*continued*)

Table 1

(continued).

First author/ Publication year	Country	Design/ Duration	n;Age (y) BMI (initial/final)	Inclusion criteria	Number of cases (initial/ final) Intervention	Number of cases (initial/ final) Comparison	Drop-out Outcomes	Adverse effect
Go'mez-D1'az[17] (2012)	Mexico	RCT/12 weeks	52/4-17 M:31.1±6.3/ 26.8 (19.39–48.2) P:27.1±5.9/ 26.1 (16.9–35.5)	Impaired glucose tolerance on OGTT per ADA criteria	n=29/28 M:850 mg twice daily Lifestyle intervention	n=28/24 Placebo and lifestyle intervention	M:1; P:4 Significant difference in resistin concentrations Significant decrease in HOMA-IR and HbA1c No change in the concentration of other markers of inflammation	M: Diarrhoea:10/28 P: Diarrhoea:0/24
MP van der Aa[18] (2016)	Netherlands	RCT/18 months	62/10-16 M:29.8 (28.1 to 34.5)/ 29.9 (26.3 to 33.6) P:30.5 (28.7 to 38.6)/ 32.8 (29.3 to 40.4)	BMI-SDS>2.3 HOMA-IR≧3.4	n=32/23 M: 1000 mg twice daily Lifestyle intervention	n=30/19 Placebo and lifestyle intervention	M:9; P:11 No significant difference was observed for HOMA-IR Improvement in fat mass BMI improved at 6–9months but was back to baseline at 18months	M: 2/32 Nausea:17/23 Diarrhoea:14/28 P:1/30 Nausea:8/19 Diarrhoea:9/19
Garibay-Nieto[19] (2016)	Mexico	RCT/16 weeks	54/8-18 M:28.54±2.8 (final) P:28.79±2.8 (final)	BMI≧95th percentile Optimal psychological health and not been previously intervened	n=24/14 M:1000mg/d Lifestyle intervention	n=30/17 Placebo and lifestyle intervention	M:12; P:13 Significant difference in insulin sensitivity Rd between CLA vs placebo Improvement in insulimia and insulin resistance	M:0/24 P:2/30
Pastor-Villaescusa[3] (2017)	Spain	RCT/6 months	160/7-14 Prepubertal M:28.2±0.6/26.5±0.7 P:29.2±0.6/28.2±0.6 Pubertal M:29.4±0.5/28.5±0.6 P:30.6±0.5/30.2±0.5	BMI>95th percentile No underlying disease or a history of pathology No medical treatment regarding weight control in the previous 12 months No participation in a previous trial	n=80/68 M:500 mg twice daily Lifestyle intervention	n=80/72 Placebo and lifestyle intervention	M:12; P:8 Significant decrease in BMI in prepubertal group Significant increments in the QUICKI, ALR, IFN-γ and PAI-1 in prepubertal childern	M: Diarrhoea:9/68 P: Diarrhoea:7/72

ALR=adiponectin–leptin ratio, ALT=alanine aminotransferase, BMI=body mass index, BMI-SDS=body mass index SD score, CLA=conjugated linoleic acid, FPG=fasting plasma glucose, HbA1c=glycosylated hemoglobin, HOMA-IR=homeostasis model assessment insulin resistance index, IFN-γ=interferon-γ, M=metformin, OGTT=oral glucose tolerance test, P=placebo, PAI-1=plasminogen activator inhibitor-1, QUICKI=quantitative insulin sensitivity check index, TNF-α=tumor necrosis factor α.

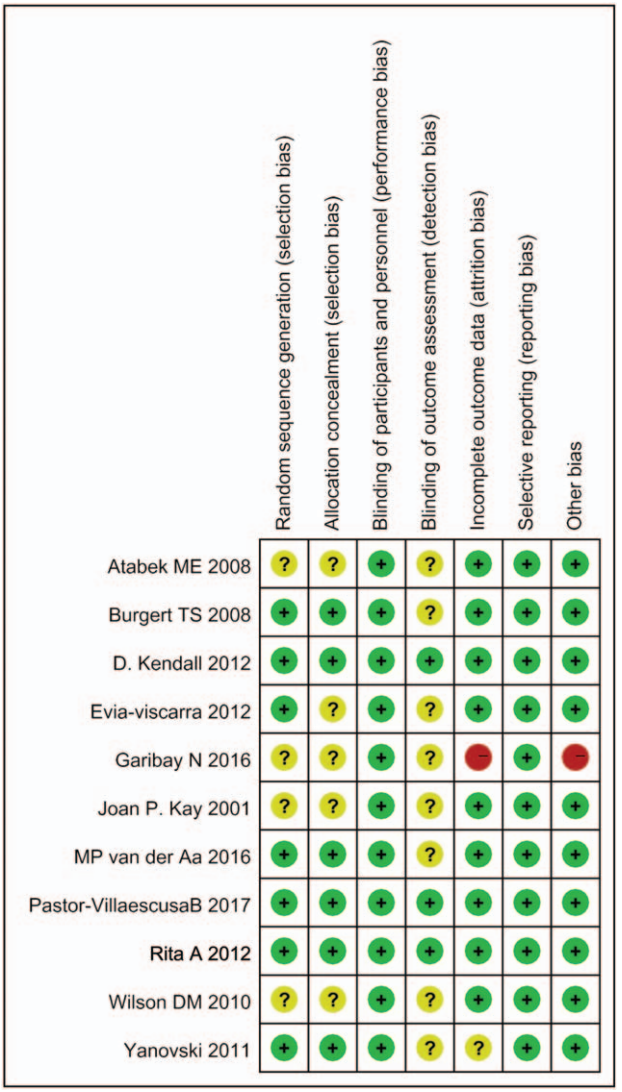

Figure 2. Risk of bias graph.

the HOMA-IR among overweight or obese children and adolescents.

3.3.2. Fasting glucose (mg/dl). In this meta-analysis, 6 studies reported the data of fasting glucose. Random effects model was used to analyze this outcome because of the moderate heterogeneity between the 2 groups ($P = .03$, $I^2 = 58\%$). Subgroup analysis was performed based on the duration of intervention. Figure 5 shows the results. When the duration of intervention was less than 6 months, there was a significant difference in reducing fasting glucose ($P = .0009$, MD = −3.59, 95%CI: −5.70, −1.48), but there was no significant difference in duration greater than or equal to 6 months ($P = .34$, MD= .89, 95%CI: −.95, 2.74).

3.3.3. Fasting insulin (uU/ml). Seven studies reported the changes in fasting insulin. The results can be seen in Figure 6. The heterogeneity between 2 groups was low ($P = .09$, $I^2 = 43\%$) and the fixed effects model was used to analyze these data. Compared with placebo, metformin combined with lifestyle intervention could lower fasting insulin ($P = .0002$, MD = −2.83, 95%CI: −4.32, −1.34).

3.3.4. HDL-C (mg/dl). Eight studies reported the data of HDL-C. The results can be seen in Figure 7. The heterogeneity between the 2 groups was low ($P = .33$, $I^2 = 12\%$), a fixed effects model was used to analyze this data. The aggregated results showed that metformin was not associated with an improvement in HDL-C ($P = .28$, MD = .63, 95%CI = −.52, 1.79).

3.3.5. LDL-C (mg/dl). Six studies investigated the changes in LDL-C. The results can be seen in Figure 8. Fixed effects model was used to analyze these outcomes because of the low heterogeneity ($P = .35$, $I^2 = 11\%$). Overall, compared with the placebo with lifestyle intervention, the therapy of metformin showed difference in lowering the LDL-C ($P = .008$, MD = −4.29, 95%CI: −7.45, −1.12).

3.3.6. Adverse events. Ten studies reported adverse events. Six of these studies described the types of adverse events and the number of people who occurred. The most frequent adverse events were abdominal pain, diarrhea, dizziness, headache, nausea, headache, and vomiting. These studies stated that the adverse events could be solved by reducing the dose of drugs and terminating medication. Four studies briefly described the number of people with adverse events. The total number of adverse events in the experimental group was 4, while the number of adverse events in the control group was 5. The solution was usually the same as mentioned in the above study.

3.3.7. Sensitivity analysis. Sensitivity analysis was performed by using the method of combined data (random or fixed effect models). The results are presented in Figures 9–12. The values of

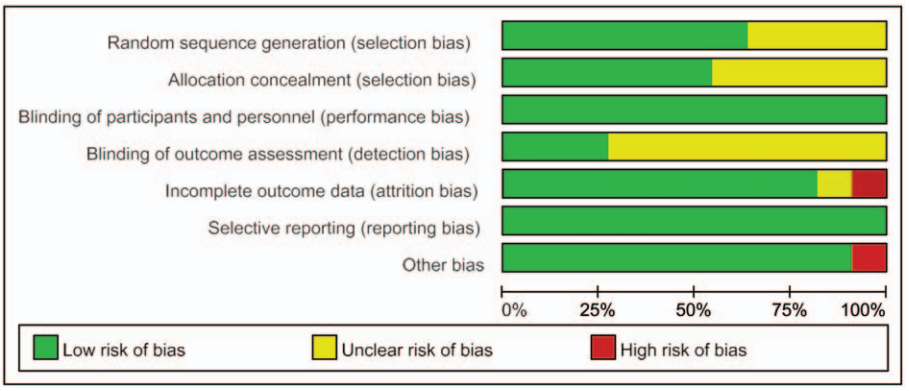

Figure 3. Risk of bias summary.

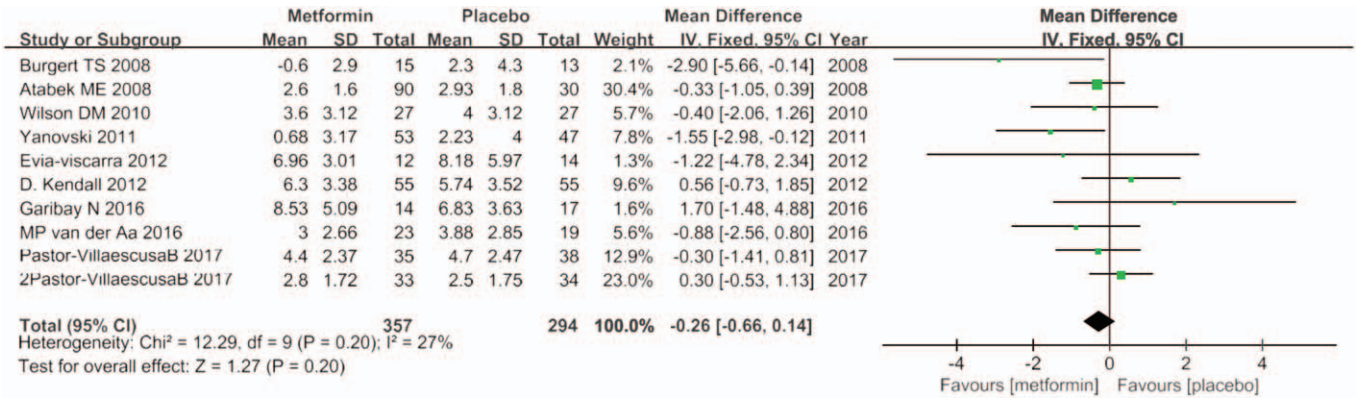

Figure 4. Change of homeostasis model assessment insulin resistance index: the result of meta-analysis.

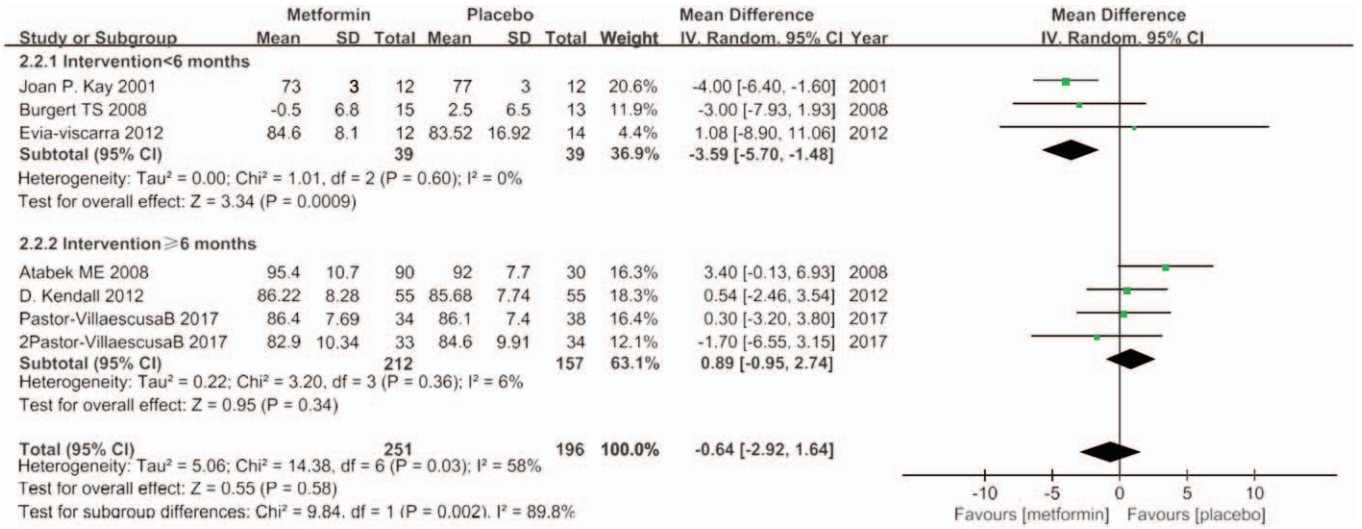

Figure 5. Change of fasting glucose: the result of meta-analysis.

MD were close in random or fixed effect models, and the overall effects were similar except for the result of fasting insulin.

3.4. Publication bias

The funnel plot of HOMA-IR can be seen in Figure 13. The result of Begg and Egger test can be seen in Figure 14. The test showed a positive result ($P_{Beggtest}$=.074, $P_{Eggertest}$=.022).

4. Discussion

Obesity is one of the major public health issues affecting people of all ages worldwide. The world has shifted from high rates of overweight and obesity in developed and industrialized countries to high rates of overweight and obesity in low- and middle-income countries.[20] It is estimated that more than 340 million children and adolescents aged 5 to 19 are obese or overweight.[2]

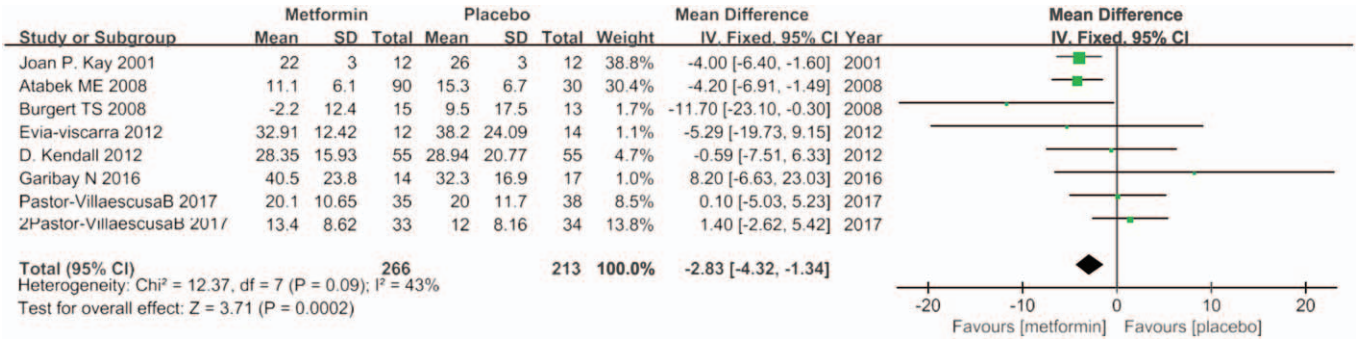

Figure 6. Change of fasting insulin: the result of meta-analysis.

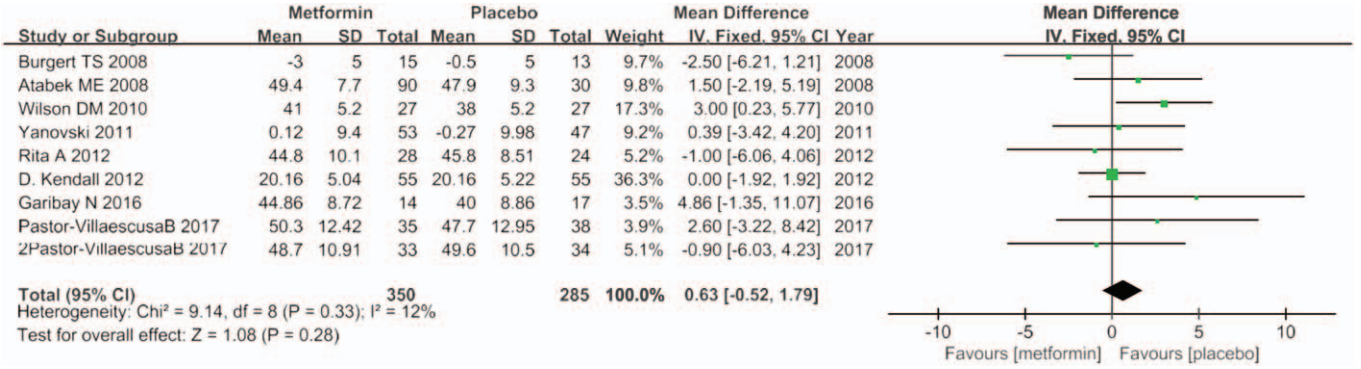

Figure 7. Change of high-density lipoprotein cholesterol: the result of meta-analysis.

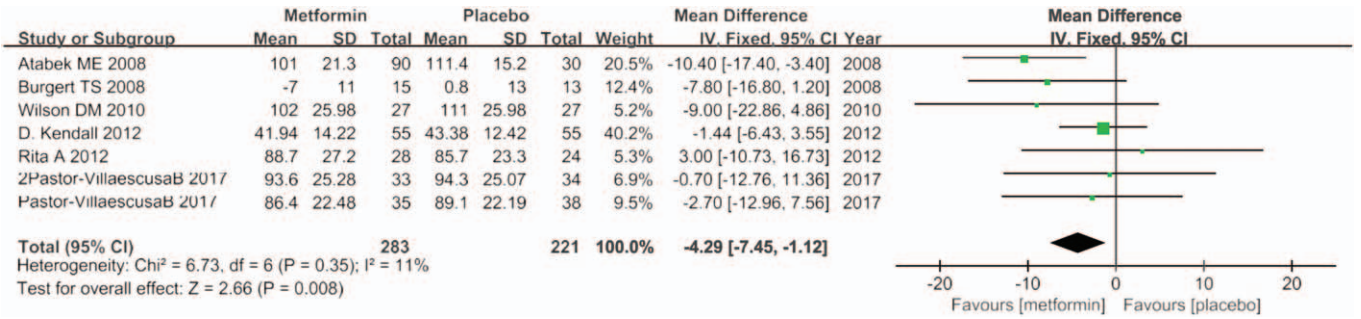

Figure 8. Change of low-density lipoprotein-cholesterol: the result of meta-analysis.

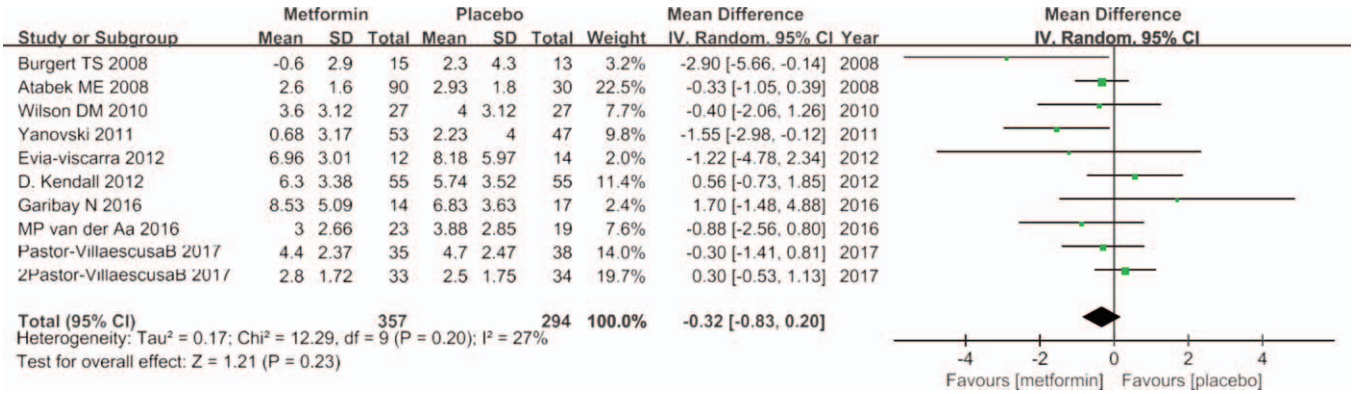

Figure 9. Sensitivity analysis results of homeostasis model assessment insulin resistance index.

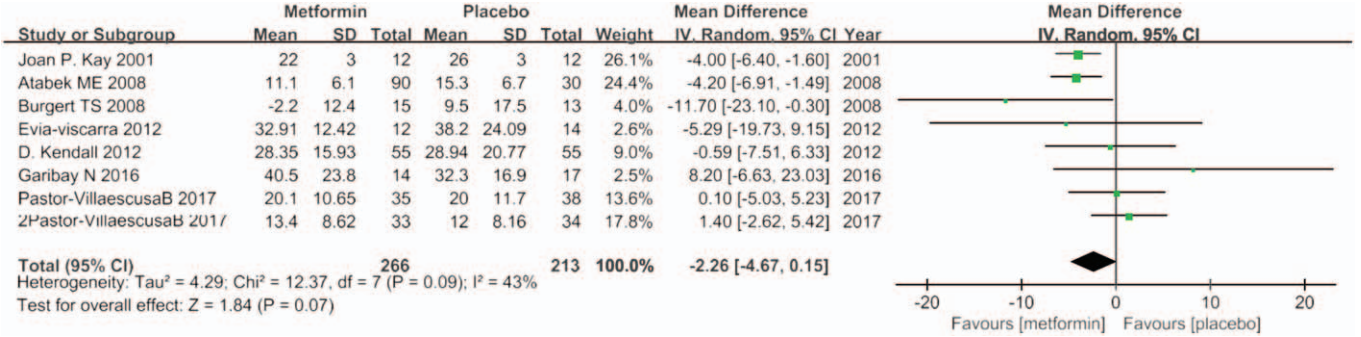

Figure 10. Sensitivity analysis results of fasting insulin.

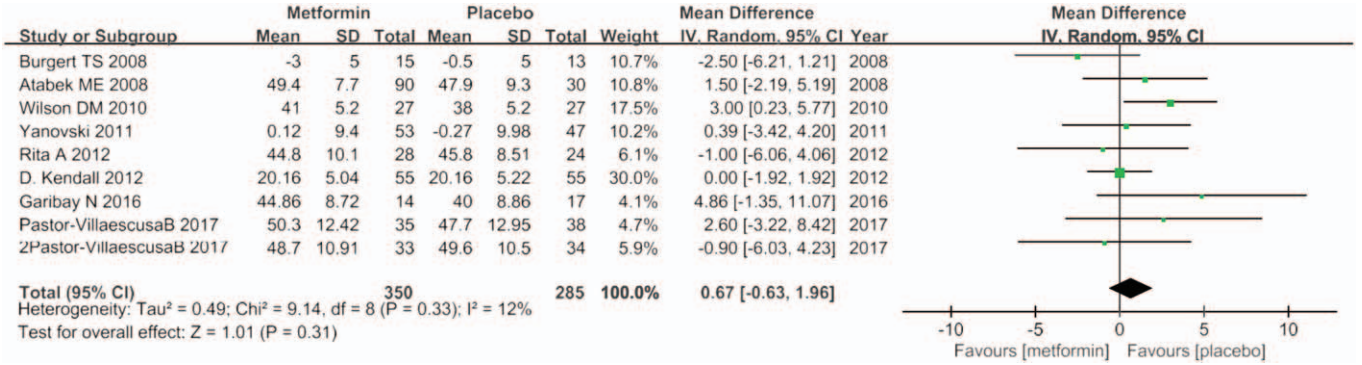

Figure 11. Sensitivity analysis results of high-density lipoprotein cholesterol.

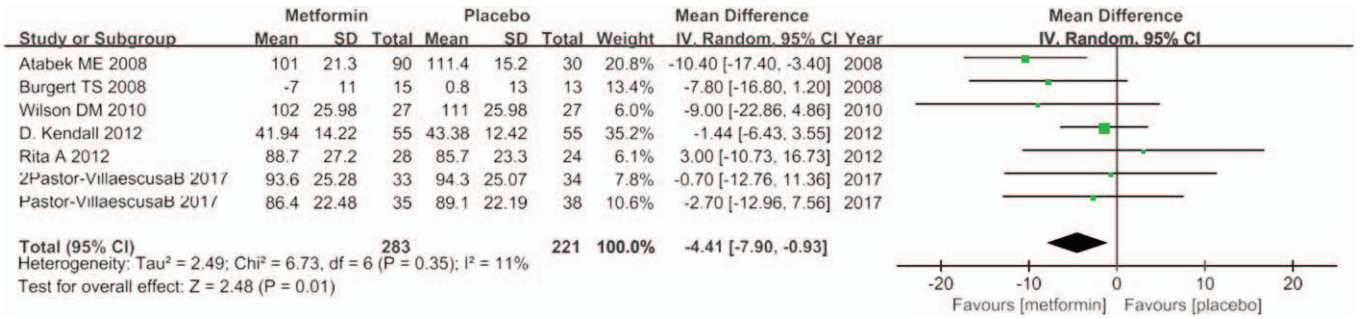

Figure 12. Sensitivity analysis results of low-density lipoprotein cholesterol.

It is well-known that overweight and obesity in children and adolescents have profound effects on both body and mind. Physical effects include hypertension, high cholesterol, metabolic syndrome, diabetes, sleep apnea, and fatty liver disease, and psychological effects include problems related to body image, self-esteem, discrimination, and depression.[21]

Combination drug therapies for obesity management are becoming more and more common in the 21st century. Medication should be used as an adjunct to treatment, especially in maintaining weight loss and treating obesity related complications.[22] Metformin is one of the drugs used to treat overweight and obesity in children and adolescents. It can lead to

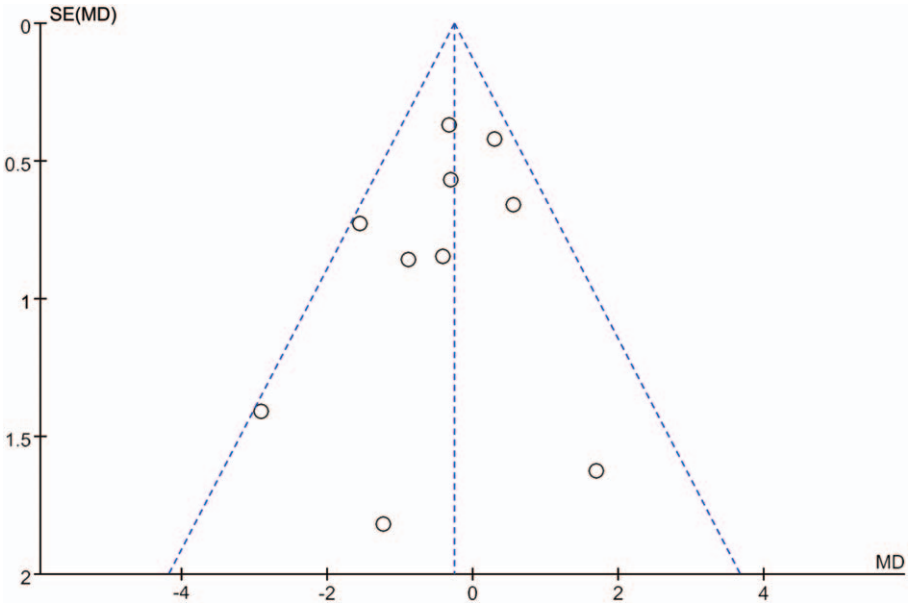

Figure 13. The funnel plot of homeostasis model assessment insulin resistance index.

Tests for Publication Bias

Begg's Test

adj. Kendall's Score (P-Q) = 21
Std. Dev. of Score = 11.18
Number of Studies = 10
z = 1.88
Pr > |z| = 0.060
z = 1.79 (continuity corrected)
Pr > |z| = 0.074 (continuity corrected)

Egger's test

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	-1.006089	1.313719	-0.77	0.466	-4.035529	2.023352
bias	2.18117	.7674712	2.84	0.022	.4113786	3.950962

Meta-analysis

Method	Pooled Est	95% CI Lower	95% CI Upper	Asymptotic z_value	Asymptotic p_value	No. of studies
Fixed	2.666	1.605	3.727	4.925	0.000	10
Random	2.666	1.605	3.727	4.925	0.000	

Test for heterogeneity: Q= 3.104 on 9 degrees of freedom (p= 0.960)

Moment-based estimate of between studies variance = 0.000

Trimming estimator: Linear

Meta-analysis type: Fixed-effects model

iteration	estimate	Tn	# to trim	diff
1	2.666	34	1	55
2	2.453	39	2	10
3	2.361	44	3	10
4	2.283	47	4	6
5	2.165	49	5	4
6	2.099	50	5	2
7	2.099	50	5	0

Filled

Meta-analysis

Method	Pooled Est	95% CI Lower	95% CI Upper	Asymptotic z_value	Asymptotic p_value	No. of studies
Fixed	2.099	1.195	3.002	4.555	0.000	15
Random	2.099	1.195	3.002	4.555	0.000	

Test for heterogeneity: Q= 7.894 on 14 degrees of freedom (p= 0.895)

Moment-based estimate of between studies variance = 0.000

Figure 14. Tests for Publication Bias.

a mild weight loss in obese pediatric patients through more scientifically sound research is needed.[23] Many studies have shown that the most common side effect of metformin is the gastrointestinal reaction, which is usually mild and can be treated by adjusting the dose.[24]

The meta-analysis revealed some interesting findings. In terms of HOMA-IR and HDL-C, compared with placebo with lifestyle intervention, metformin showed no significant reduction. Metformin did not improve insulin resistance. For fasting glucose, we performed subgroup analysis based on the duration

of the intervention. Metformin was effective in reducing the levels of fasting glucose when the duration was less than 6 months ($P = .0009$). Once the duration of the intervention was greater than or equal to 6 months, this effect would no longer be significant($P = .58$), possibly due to a decrease in the number of participants, a change in treatment adherence or a decrease in the effectiveness of metformin after 6 months. Regarding fasting insulin and LDL-C, our result showed a decrease in the metformin group. The mechanism was still unclear, probably because metformin had anti-lipid oxidative effect and reduced the degree of lipid peroxidation of LDL-C. As for adverse effects, 10 studies mentioned adverse effects. Common side effects were gastrointestinal discomfort, including abdominal pain, diarrhea, nausea, vomiting.

In terms of sensitivity analysis, we used the method of combined data (random or fixed effect models) to test reliability of conclusion. For the fasting insulin, the value of MD and the overall affect were different after changing the effected model. Considering Garibay N's study which had two dimensions suggesting high risk bias affected the reliability of conclusion, we removed the study and analyzed it, the combined effect size changed from −2.26 (−4.67 to .15) to −2.55 (−4.85 to −.25). It could be considered that this study affected the robustness of the conclusion. Whether metformin could improve fasting insulin in overweight or obese children and adolescents needed to be confirmed by more high quality studies.

With regard to publication bias, Begg test and Egger test were performed to detect publication bias. For HOMA-IR, the results of the Begg test and the Egger test were contradictory. Begg test showed no publication bias, and Egger test had. At the same time, we also used the trim and fill method to check for publication bias. As shown in Figure 14. This method indicated no publication bias. The reasons for these differences might be due to the small number of studies included in the analysis.

However, the systematic review also had some limitations. First, 11 studies were included, while 3 of them had small sample sizes, the result might be overestimated. Second, the data in this meta-analysis was only from published literature, considering that some studies with negative results had not been published in time, leading to publication bias. These negative findings suggested that metformin had no effect on HOMA-IR, fasting blood glucose, fasting insulin, LDL-C, and HDL-C might affect the results of this study. The number of studies included in the meta-analysis was small, and the funnel plot used to detect the publication bias was of little significance. Last but not the least, there might be omissions in document retrieval and inclusion because of the limits of language and retrieval. The principle of random allocation, allocation concealment, and blinding were not described in detail in some of the included studies. Therefore, a larger sample size and more adequate data were needed to assess the effectiveness and safety of future treatments.

5. Conclusions

This meta-analysis suggests that metformin treatment may improve the level of LDL-C. It shows no significant improvement in insulin resistance, fasting glucose, and HDL-C. In terms of fasting insulin, the sensitivity analysis suggests that the results of meta-analysis lack reliability. Whether metformin could improve fasting insulin is still inconclusive. Given the potential limitations of meta-analysis, in the future, larger samples and high-quality RCT studies are needed to confirm these conclusions.

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References

[1] Word Health Organization Childhood overweight and obesity. WHO. http://www.who.int/dietphysicalactivity/childhood/en/. (Accessed on 26 June 2018).
[2] Word Health Organization Obesity and overweight. WHO. http://www.who.int/en/news-room/fact-sheets/detail/obesity-and-overweight. (Accessed on 9 July 2018).
[3] Pastor-Villaescusa B, Cañete MD, Caballero-Villarraso J, et al. Metformin for obesity in prepubertal and pubertal children: a randomized controlled trial. Pediatrics 2017;140: e20164285.
[4] Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002;346:393–403.
[5] Kelly AS, Fox CK, Rudser KD, et al. Pediatric obesity pharmacotherapy: current state of the field, review of the literature and clinical trial considerations. Int J Obes (Lond) 2016;40:1043–50.
[6] Hearnshaw C, Matyka K. Managing childhood obesity: when lifestyle change is not enough. Diabetes Obes Metab 2010;12:947–57.
[7] Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.
[8] Ades AE, Lu G, Higgins JP. The interpretation of random-effects meta-analysis in decision models. Med Decis Making 2005;25: 646–54.
[9] Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60.
[10] Kay JP, Alemzadeh R, Langley G, et al. Beneficial effects of metformin in normoglycemic morbidly obese adolescents. Metabolism 2001;50:1457–61.
[11] Atabek ME, Pirgon O. Use of metformin in obese adolescents with hyperinsulinemia: a 6-month, randomized, double-blind, placebo-controlled clinical trial. J Pediatr Endocrinol Metab 2008;21: 339–48.
[12] Burgert TS, Duran EJ, Goldberg-Gell R, et al. Short-term metabolic and cardiovascular effects of metformin in markedly obese adolescents with normal glucose tolerance. Pediatr Diabetes 2008;9:567–76.
[13] Wilson DM, Abrams SH, Aye T, et al. Metformin extended release treatment of adolescent obesity: a 48-week randomized, double-blind, placebo-controlled trial with 48-week follow-up. Arch Pediatr Adolesc Med 2010;164:116–23.
[14] Yanovski JA, Krakoff J, Salaita CG, et al. Effects of metformin on body weight and body composition in obese insulin-resistant children: a randomized clinical trial. Diabetes 2011;60:477–85.
[15] Evia-Viscarra ML, Rodea-Montero ER, Apolinar-Jimenez E, et al. The effects of metformin on inflammatory mediators in obese adolescents with insulin resistance: controlled randomized clinical trial. J Pediatr Endocrinol Metab 2012;25:41–9.
[16] Kendall D, Vail A, Amin R, et al. Metformin in obese children and adolescents: the MOCA trial. J Clin Endocrinol Metab 2013;98:322–9.
[17] Gomez-Diaz RA, Talavera JO, Pool EC, et al. Metformin decreases plasma resistin concentrations in pediatric patients with impaired glucose tolerance: a placebo-controlled randomized clinical trial. Metabolism 2012;61:1247–55.

[18] van der Aa MP, Elst MA, van de Garde EM, et al. Long-term treatment with metformin in obese, insulin-resistant adolescents: results of a randomized double-blinded placebo-controlled trial. Nutr Diabetes 2016;6:e228.
[19] Garibay-Nieto N, Queipo-Garcia G, Alvarez F, et al. Effects of conjugated linoleic acid and metformin on insulin sensitivity in obese children: randomized clinical trial. J Clin Endocrinol Metab 2017;102:132–40.
[20] Greydanus DE, Agana M, Kamboj MK, et al. Pediatric obesity: current concepts. Dis Mon 2018;64:98–156.
[21] Pulgaron ER. Childhood obesity: a review of increased risk for physical and psychological comorbidities. Clin Ther 2013;35: A18–32.
[22] Steinbeck KS, Lister NB, Gow ML, et al. Treatment of adolescent obesity. Nat Rev Endocrinol 2018;14:331–44.
[23] Mead E, Atkinson G, Richter B, et al. Drug interventions for the treatment of obesity in children and adolescents. Cochrane Database Syst Rev 2016;11:Cd012436.
[24] Boland CL, Harris JB, Harris KB. Pharmacological management of obesity in pediatric patients. Ann Pharmacother 2015;49:220–32.