



Metformin for Weight Gain Associated with Second-Generation Antipsychotics in Children and Adolescents: A Systematic Review and Meta-Analysis

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Abstract

Background Weight gain is a potentially concerning side effect of second-generation antipsychotics (SGAs). Metformin, a biguanide with antihyperglycemic effects, is used to manage weight gain in adults treated with SGAs.

Objective The objective of this study was to perform the first systematic review and meta-analysis of randomized controlled trials (RCTs) assessing the effects of metformin on weight gain in children and adolescents treated with SGAs.

Methods Based on a pre-registered protocol (PROSPERO–CRD42017074839), we searched the PubMed, EMBASE, PsycINFO, BIOSIS, Science Direct, Cochrane Central, and ClinicalTrials.gov electronic databases through March 2018 (with no restrictions on language, date, or type of publication) for RCTs that assessed the effect of metformin or placebo on body weight in children or adolescents (< 18 years of age) treated with selected SGAs (risperidone, aripiprazole, olanzapine, and clozapine) for any psychiatric disorder. We also contacted relevant drug manufacturers for possible additional pertinent studies/data. A random effects model was used and the quality of the included RCTs was assessed using the Cochrane Risk of Bias tool.

Results Five RCTs (205 participants in total) were included in the meta-analysis. We found a significant weight decrease in the metformin group compared with placebo after 4, 12, and 16 weeks of treatment {mean difference – 0.98 kg (95% confidence interval [CI] – 1.26, – 0.69); – 1.83 kg (95% CI – 2.47, – 1.18); and – 3.23 kg (95% CI – 5.59, – 0.86), respectively}. A weight decrease at weeks 2 and 8 did not reach statistical significance. The decrease in body mass index (BMI) paralleled that of weight, with a significant effect at weeks 4, 12, and 16. Overall, four studies were rated as unclear, and one study was rated as high, risk of bias.

Conclusion Meta-analytical evidence shows that metformin might decrease weight in children/adolescents treated with SGAs but additional high-quality evidence is needed. Clinicians need to be aware that this use of metformin is currently off-label.

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Key Points

This is the first systematic review and meta-analysis exploring the efficacy of metformin to manage weight gain and body mass index (BMI) increase related to the administration of second-generation antipsychotics (SGAs) in the pediatric population.

From 12 weeks of treatment, metformin was significantly more efficacious than placebo in reducing BMI in children and adolescents treated with SGAs.

1 Introduction

In children and adolescents, second-generation antipsychotics (SGAs) are US FDA-approved for a number of indications in mental health conditions, including autism spectrum disorder, schizophrenia, and bipolar disorder, and are widely used off-label in Tourette's syndrome and disruptive behavior associated with externalizing disorders [1–4]. Over the past decades, there has been a remarkable increase in the prescription of SGAs across several countries [5–8]. Indeed, SGAs are among the most commonly prescribed medications in children and adolescents in North America [4]. Unfortunately, these drugs are associated with important adverse effects, including weight gain and metabolic disturbances [9, 10]. In the Second-generation Antipsychotic Treatment Indications, Effectiveness and Tolerability in Youth (SATIETY), a large naturalistic cohort study conducted from 2001 to 2007, a weight gain of more than 7% was observed during the first 3 months for 85% of patients treated with olanzapine, 65% of patients treated with risperidone, and 60% of patients treated with aripiprazole [11]. These results have been confirmed by recent meta-analytic evidence [12].

Obesity in children and adolescents is associated with a dramatic increase in morbidity. Approximately 25% of youth with obesity present with metabolic syndrome and increased risk for atherosclerosis, heart diseases, and type 2 diabetes mellitus [13–15]. The risk of heart disease is tenfold higher in youth with obesity compared with healthy-weight peers [16]. Children and adolescents with obesity may also experience psychological distress related to being bullied, leading to poor self-image and possibly depression [17]; thus, careful screening and early interventions to prevent weight gain and metabolic syndrome are recommended in youth treated with SGAs [18]. Unfortunately, in clinical practice, careful metabolic parameter monitoring is often overlooked in youth treated with SGAs [19]. Non-pharmacological strategies for weight gain, such as educational or family-based

interventions, are recommended but showed limited efficacy. Supporting evidence on their effects have been extrapolated from studies of children with obesity or type 2 diabetes mellitus [20]. In 1999, metformin was proposed as a promising pharmacological option to manage weight gain associated with the use of SGAs, although use for this purpose was, and remains, off-label [21]. Metformin is currently approved by both the FDA and the European Medicines Agency (EMA) for treating type 2 diabetes mellitus in children older than 10 years of age [22, 23]; however, in this specific indication, lifestyle interventions are more effective than metformin for preventing progress from pre-diabetes to diabetes, and inducing weight loss [24]. This drug is also effective in reducing the body mass index (BMI) of children with obesity [25]. Meta-analytic evidence shows that metformin combined with lifestyle interventions was efficacious (albeit with moderate effect size) and well tolerated in decreasing weight in children with obesity aged 10–16 years [26, 27]. Additionally, in adults, metformin has been found to be efficacious in improving both glycemic control and weight gain related to SGAs. It is important to note that this effect is reported in studies of relatively short duration, especially in patients who are already obese [28–31]. There is also preliminary but increasing evidence on the use of metformin in childhood to manage the metabolic disturbances induced by SGAs, including weight gain [32, 33]. To our knowledge, no systematic review and meta-analysis has been conducted to estimate the efficacy of metformin in counteracting the effects of SGAs on weight in children and adolescents, and our study aimed to fill this gap. Given the exploratory nature of this meta-analysis, no a priori hypothesis was formulated.

2 Methods

2.1 Search Strategy

The protocol for the present systematic review/meta-analysis was registered on the international prospective register of systematic reviews (PROSPERO; <https://www.crd.york.ac.uk/PROSPERO>, protocol number CRD42017074839). This systematic review and meta-analysis was conducted and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations [34]. The PubMed (MEDLINE), EMBASE, PsycINFO, BIOSIS, Science Direct, and Cochrane CENTRAL electronic databases were searched, with no restriction in terms of language, type of document, or date; the following search terms/syntax were used for Pubmed: metformin AND (antipsychotic* OR Risperidone OR Aripiprazole OR Olanzapine OR Clozapine) AND (child OR children OR adolesc* OR youth* OR pediater* OR paediatric* OR early onset). In our search terms, we specified the risperidone, aripiprazole,

olanzapine, and clozapine SGAs because these are the most widely used drugs of this class in the pediatric population and/or those most associated with metabolic side effects. The search terms/syntax were adapted accordingly for all the remaining databases. Reference lists of the retained articles and relevant review articles were hand-searched to retrieve any additional pertinent reports not detected via the electronic database search. Furthermore, we searched the ClinicalTrials.gov database to retrieve any pertinent studies not yet published as full-text articles at the time of our search. The last search was completed on 30 March 2018. Additionally, we contacted relevant drug manufacturers to inquire about any relevant published or unpublished studies not identified in our search.

2.2 Selection of Relevant Articles

Studies were included in our systematic review if they met the following criteria: (1) randomized controlled trials (RCTs), regardless of the level of blinding and follow-up time; (2) participants under the age of 18 years; (3) participants treated with any SGAs and randomized to metformin or placebo, whatever the type of psychiatric disorder for which they received the antipsychotic; and (4) weight and/or BMI values at baseline and study endpoint as study outcomes. All non-randomized studies were excluded, and no restrictions in terms of the ethnic origin of participants were applied.

2.3 Selection of Studies and Data Extraction

The eligibility process was conducted in two separate stages. First, two researchers (PE and RD) independently screened all non-duplicate references initially retrieved as potentially pertinent, and excluded those clearly not pertinent based on title or abstract. A final list was agreed on, with discrepancies resolved by consensus between the two authors. When consensus was not reached, a third senior researcher (SC) acted as arbitrator. Second, full-text versions of the articles passing stage 1 screening were downloaded and independently assessed for eligibility by the two researchers. Discrepancies were resolved by consensus between the two researchers and, if needed, the third senior researcher acted as arbitrator. When required, corresponding authors were contacted to clarify study eligibility.

2.4 Risk of Bias of Included Studies

Risk of bias for each study included in the meta-analysis was assessed using the Cochrane Risk of Bias Tool [35]. Risk of bias domains included selection bias (random sequence generation, allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding

of outcome assessment), attrition bias (incomplete outcome data), reporting bias (selective reporting), and other bias. As in the work by Cortese [36], the overall rating of risk of bias for each study was the lowest rating for any of the criteria (e.g. if any item was scored as high risk of bias, the entire study was scored as high risk of bias; if all items were scored as low risk, the entire study overall was rated as low risk).

2.5 Statistical Analyses

The mean difference (MD) for each study was first calculated as the mean pre- to post-treatment change in the intervention group minus the mean pre- to post-treatment change in the control group, divided by the pooled pre-test standard deviation with bias adjustment [37]. Analyses were conducted as per protocol data, with the exception of one study [38] that presented data for intention-to-treat analyses only. The MD for each trial was then combined using the inverse variance method. Given the inherent heterogeneity of studies, a random effects model was used. The I^2 statistic (representing the percentage of variance due to between-study heterogeneity rather than sampling error [39]) was calculated to estimate between-trial MD heterogeneity. Analyses were performed using RevManager 5 (<http://community.cochrane.org/help/tools-and-software/revman-5>).

3 Results

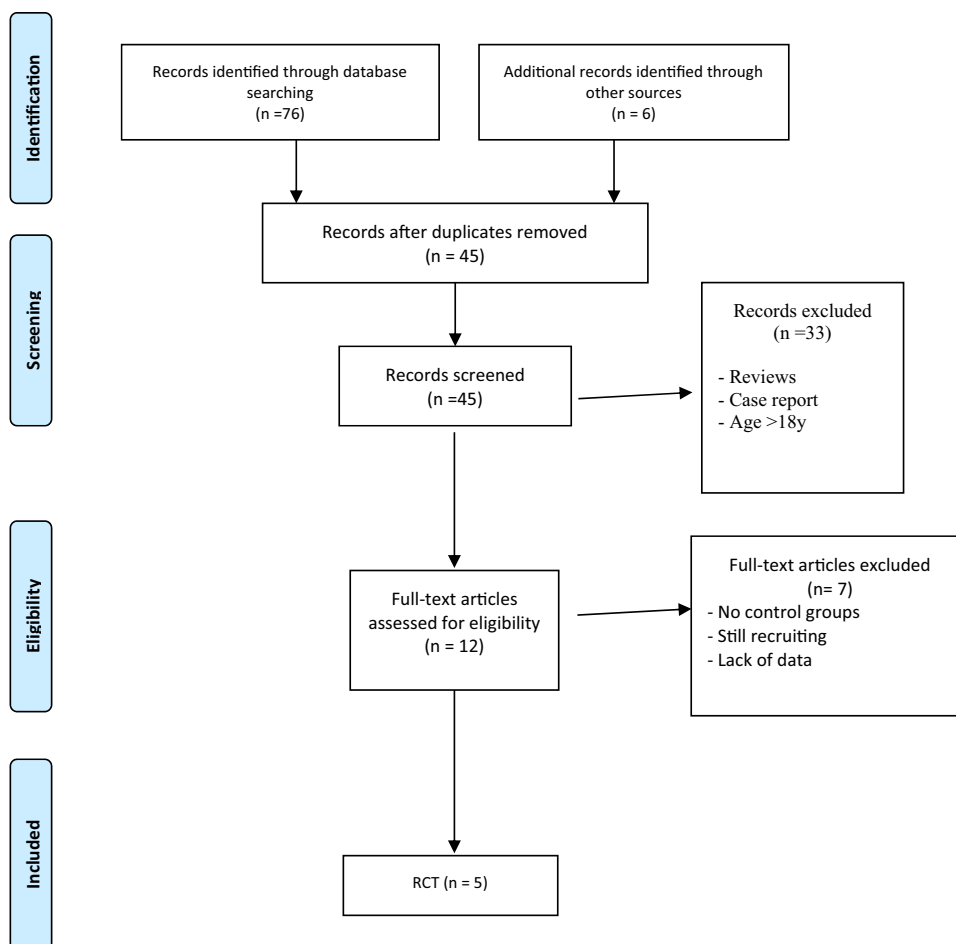
3.1 Search Strategy

From an initial pool of 76 potentially relevant references, five studies were included in the meta-analysis [38, 40–43]. Figure 1 reports the PRISMA flowchart detailing the screening process, and Electronic Supplementary Table 1 reports the references discarded after reading the full text, with the specific reasons for exclusion.

3.2 Characteristics of Studies Included in the Meta-Analysis

Three studies were published as full-text reports in peer-reviewed journals [38, 40, 41] and two additional studies were found on ClinicalTrials.gov [42, 43] (Table 1). The duration of the studies varied from 16 to 26 weeks. For all studies, both weight and BMI values (at baseline and endpoint) were available. The age range of participants was between 11.25 and 14.2 years.

Fig. 1 PRISMA flowchart reporting the study screening process. *RCT* randomized controlled trial



3.3 Results of the Meta-Analysis

3.3.1 Effect of Metformin on Weight

Meta-analysis results on weight gain are reported in Figs. 2, 3, and 4. The difference in weight change between metformin and placebo from baseline to weeks 2 and 8 did not reach statistical significance {MD – 0.29 (95% confidence interval [CI] – 1.00, 0.41); and – 1.54 (95% CI – 3.52, 0.45), respectively}. There was evidence of heterogeneity at week 2 [$\tau^2=0.16$, $\text{Chi}^2=2.67$, degrees of freedom (df)=1 ($p=0.10$), $I^2=63\%$] and week 8 [$\tau^2=1.28$, $\text{Chi}^2=2.55$, $df=1$ ($p=0.11$), $I^2=61\%$]. The difference between metformin and placebo in weight change from baseline to weeks 4, 12, and 16 was significant [– 0.98 (95% CI – 1.26, – 0.69); – 1.83 (95% CI – 2.47, – 1.18); and – 3.23 (95% CI – 5.59, – 0.86), respectively]. Heterogeneity values at weeks 4, 12, and 16 were $\tau^2=0.01$, $\text{Chi}^2=2.10$, $df=2$ ($p=0.35$), $I^2=5\%$; $\tau^2=0.00$, $\text{Chi}^2=2.16$, $df=3$ ($p=0.54$), $I^2=0\%$; and $\tau^2=1.20$, $\text{Chi}^2=1.41$, $df=1$ ($p=0.24$), $I^2=29\%$, respectively.

3.3.2 Effect of Metformin on Body Mass Index

The results of the meta-analysis on BMI are reported in Figs. 5 and 6. Results paralleled those for weight, with no statistical significance at week 4 [– 0.29 (95% CI – 0.59, 0.01)], but significant values at weeks 12 and 16 [– 0.63 (95% CI – 0.86, – 0.40) and – 1.00 (95% CI – 1.54, – 0.46), respectively] between weight changes in the metformin and placebo groups. Heterogeneity values at weeks 4, 12, and 16 were $\tau^2=0.04$, $\text{Chi}^2=4.20$, $df=1$ ($p=0.04$), $I^2=76\%$; $\tau^2=0.00$, $\text{Chi}^2=0.11$, $df=2$ ($p=0.95$), $I^2=0\%$; and $\tau^2=0.03$, $\text{Chi}^2=1.16$, $df=1$ ($p=0.28$), $I^2=14\%$, respectively.

3.4 Risk of Bias

As shown in Table 2, one study [43] was, overall, deemed as high risk of bias, whereas the others were rated as unclear risk of bias overall [37, 39–41].

Table 1 Studies included in the meta-analysis

Studies	Country	N of patient	Ratio M/F	Mean age (years)	SD	N of control	Ratio M/F	Mean age	SD	Type of patient	Type of analysis	Metformin dosage (mg/day)	Time point (w)
Anagnostou et al. [38]	Canada/USA	28	21/07	12.9	2.85	32	24/08	12.7	2.64	> 7% BMI increase in the last year	Intention to treat	1000–1500 (mean 1293.5)	4,8,12,16
Klein et al. [40]	USA	18	09/09	12.9	2.4	20	12/8	13.4	2.4	> 10% weight gain in the last year	Per protocol	1700	4,12
Arman et al. [41]	Iran	16	11/05	11.25	2.46	16	10/05	8.9	4.28	Preventive	Per protocol	1000	16
NCT00617240 [42]	USA	5	2/3	14.2	1.643	4	3/1	14.25	2.754	Preventive	Per protocol	250–2000	24
NCT00806234 [43]	USA	49	31/18	13.4	3.2	47	30/17	13.4	1.4	BMI > 85th percentile	Per protocol	500–2000	26

M male, F female, SD standard deviation, BMI body mass index

3.5 Changes in Relation to the Original Protocol

Given the paucity of available data, we were unable to conduct the planned analysis on the effect of metformin on glucose and cholesterol parameters, or on the tolerability of metformin.

4 Discussion

To our knowledge, this is the first systematic review and meta-analysis exploring the efficacy of metformin in counteracting weight gain and BMI increase related to the administration of SGAs in the juvenile population. Our meta-analysis showed that from 12 weeks of treatment, metformin was significantly more efficacious than placebo in reducing BMI in children and adolescents treated with SGAs. Our results are in agreement with those results in adults where the efficacy of metformin in reducing weight gain was demonstrated by several meta-analyses [28, 44–46]. Although our meta-analysis could not provide additional information beyond week 16, preliminary evidence from an open-label study suggested that the effect was maintained after 16 weeks of treatment [47]. It is also fundamental to note that metformin is used off-label in this indication in psychiatry. In addition, a 10-year follow-up study of the Diabetes Prevention Program Research Group has shown that a lifestyle intervention program is more efficacious than metformin for weight loss [24]. Even if the efficacy of metformin in adult populations exposed to SGAs is more robust, it is recommended that it never be used before healthy lifestyle interventions [48, 49].

The exact mechanisms underlying the effects of metformin in reducing weight gain related to antipsychotic treatment remain to be elucidated. Metformin is a biguanide that has been found to inhibit hepatic glucose production, lower circulating free fatty acids, and, ultimately, reduce gluconeogenesis and intestinal absorption of glucose [50]. It also improves the uptake of glucose and its use by the muscle instead of adipocytes [51]. The main mechanism of weight loss may result from a reduction of insulin resistance and an increase in the sense of satiety [52]. Finally, one cannot exclude that gastrointestinal distress induced by metformin may also be one of the mechanisms leading to weight loss in patients. In the specific context of SGA use, the efficacy of metformin might be accounted for by these two mechanisms [53]. Of note, a recent study showed that only half of the weight gain observed in youth taking antipsychotics is fat [54]. Metformin attenuation of weight gain might represent some attenuation of fat increase and some attenuation of lean mass (muscle and/or water). Because these mechanisms are mostly speculative, further research is needed to gain insight into the precise mechanism of action of metformin in patients treated with SGAs.

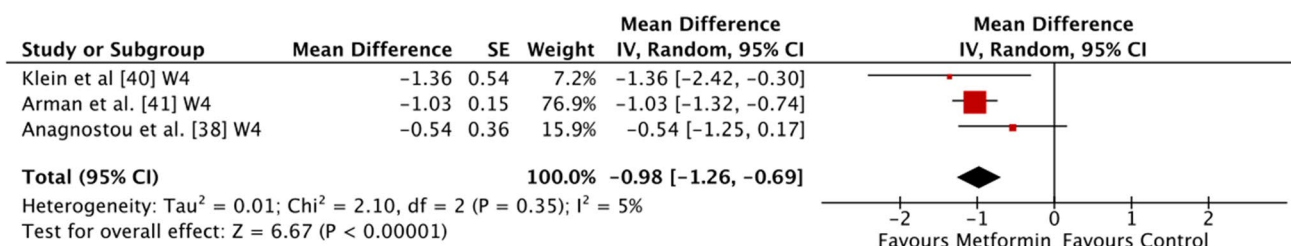


Fig. 2 Forest plot relative to the comparison of metformin versus placebo on weight loss at week 4. *W4* week 4, *SE* standard error, *CI* confidence interval, *df* degrees of freedom, *IV* inverse variance

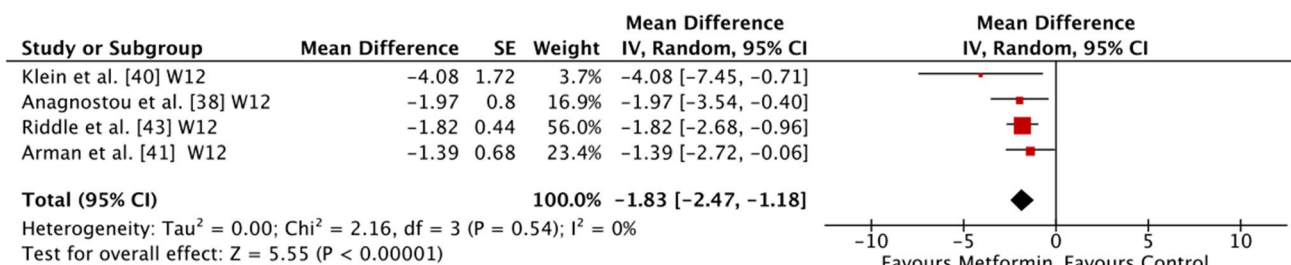


Fig. 3 Forest plot relative to the comparison of metformin versus placebo on weight loss at week 12. *W12* week 12, *SE* standard error, *CI* confidence interval, *df* degrees of freedom, *IV* inverse variance

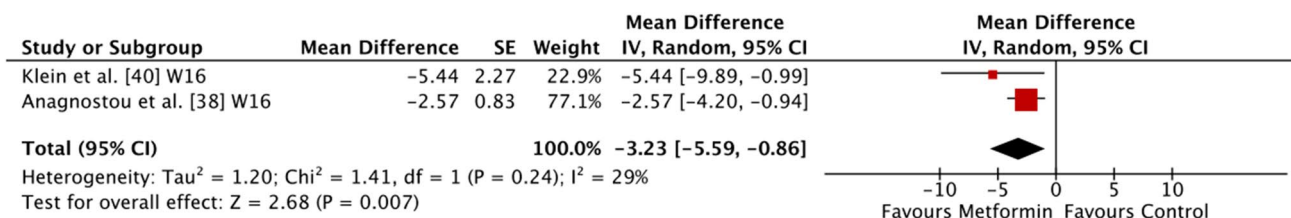


Fig. 4 Forest plot relative to the comparison of metformin versus placebo on weight loss at week 16. *W16* week 16, *SE* standard error, *CI* confidence interval, *df* degrees of freedom, *IV* inverse variance

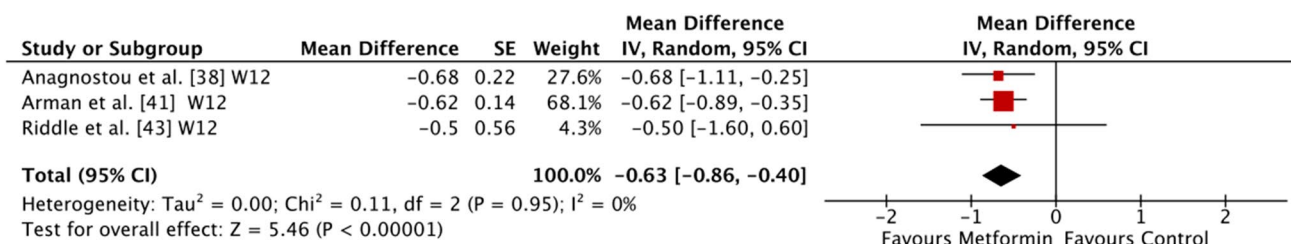


Fig. 5 Forest plot relative to the comparison of metformin versus placebo on body mass index at week 12. *W12* week 12, *SE* standard error, *CI* confidence interval, *df* degrees of freedom, *IV* inverse variance

Our results should be considered in light of the strengths and limitations of this study. Regarding the strengths, we performed a systematic search of several databases, without language restrictions, including ClinicalTrials.gov. We also contacted the studies' authors and drug companies to

gather additional unpublished data. However, a number of limitations should be taken into account. First, we could only retain a limited number of studies that explored the effects of metformin in the pediatric populations. However, there is no established minimum number of studies to be included in

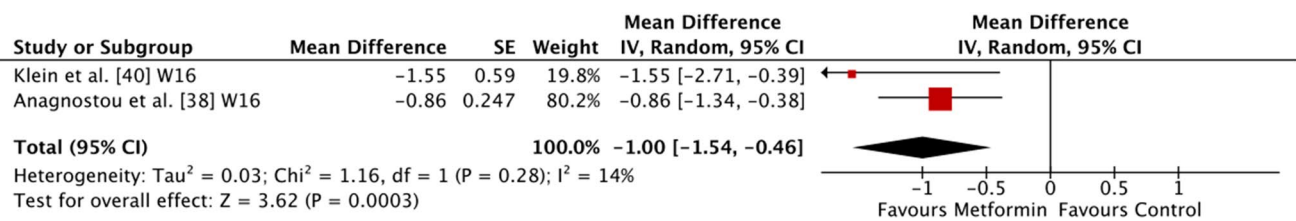


Fig. 6 Forest plot relative to the comparison of metformin versus placebo on body mass index at week 16. *W16* week 16, *SE* standard error, *CI* confidence interval, *df* degrees of freedom, *IV* inverse variance

a meta-analysis [54], and, given the high clinical relevance of the topic, this first evidence synthesis in the field should hopefully encourage further methodologically sound investigations. Second, none of the included studies were, overall, rated as low risk of bias, with the majority ($n = 4$) of studies overall rated as unclear risk of bias, and one study rated as high risk of bias. However, it should be noted that we used stringent criteria to rate the risk of bias (a study had to present all items at low risk of bias in order to be rated, overall, as low risk of bias). Furthermore, many items were rated as unclear due to missing information in the publication, which calls for better and more complete reporting in the field. Third, due to the paucity of data, we did not perform subgroup analysis based on the type of SGA. For similar reasons, we were unable to perform subgroup analysis by preventative or curative use of metformin (whatever the specific mental health conditions for which SGAs were prescribed). However, unlike studies in adults, all SGAs have been associated with significant metabolic alterations in children and adolescents [55]. Furthermore, we were not able to meta-analyze the outcome on the tolerability of metformin; however, evidence from non-randomized studies is available to inform prescribers on this relevant issue. For instance, in a long-term follow-up study of 6.5 years on 700 pediatric

patients treated with metformin, 40% presented with mild gastrointestinal symptoms (such as abdominal pain, nausea, metallic taste, bloating, and diarrhea), 20% presented with anemia, and 5.7% showed elevated liver transaminases [56]. Clinicians must be aware of the high rate of gastrointestinal distress, which can be a major issue in treatment adherence. Long-term use of metformin was also associated with a decreased in vitamin B12 [32]. The overall adverse event rate was estimated at 5.6% participant-years of exposure [56]. In adults, a study on 47,597 patients during a follow-up period of 7.2 ± 3.2 years showed that the long-term use of metformin was associated with a significant decrease in colorectal cancer occurrence [57]. These results were replicated in another cohort [58]. More generally, in a cohort including 82,720 adult metformin users, long-term adherence to metformin was associated with decreased risks of all-cause mortality after a 2.4-year follow-up period [59]. However, caution is required in the pediatric context, especially in relation to the use of metformin for weight gain prevention related to SGA treatment, considering the possible risks of metformin and the fact that the non-pharmacological alternatives have been found to be effective. However, in situations where non-pharmacological approaches are not feasible or are unsuccessful, metformin may be considered as

Table 2 Cochrane risk of bias tool for studies retained in the meta-analysis

Study, year	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other sources of bias	Overall
Klein et al., 2006 [40]	Unclear	Unclear	Unclear	Low	Low	Unclear	Low	Unclear
Arman et al., 2008 [41]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Anagnostou et al., 2016 [38]	Low	Low	Low	Low	Unclear	Low	Low	Unclear
NCT00806234 [43]	Unclear	Unclear	High	Low	Unclear	Low	Low	High
NCT00617240 [42]	Unclear	Unclear	Low	Low	Unclear	Low	Low	Unclear

a possible intervention, supported by preliminary evidence, as shown in this meta-analysis. Of note, no serious adverse events were reported in any of the studies included in our meta-analysis.

5 Conclusions

Our study provided meta-analytic evidence that metformin may be beneficial, in the short term, to counteract weight gain in children and adolescents treated with SGAs. However, our findings should be replicated in larger trials before being considered for supporting clinical recommendations, and should be considered with caution due to the low number of studies (with a low number of participants) included, the overall heterogeneity between studies, and the off-label use of metformin [43, 60–65]. If replicated in further large, high-quality trials, our findings suggest that since it took approximately 4 weeks for significant effects to be observed, early administration of metformin, soon after the patient is started on an SGA, would be warranted, reflecting the currently available guidelines for adults [66]. It is important to bear in mind that the American Psychiatric Association recommends that antipsychotic medications should not be routinely prescribed as a first-line intervention for children and adolescents, which is actually the best way to avoid metabolic side effects [67]. Multimodal treatment strategies encompassing metformin and non-pharmacological strategies (such as diet and educational or family-based interventions) are likely to represent the most efficacious intervention to counteract weight gain associated with SGAs in youth, and should be a research priority in this field.

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Compliance with Ethical Standards

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Conflicts of interest Pierre Ellul and Richard Delorme declare no conflicts of interest. Samuele Cortese has received fees from the Association for Child and Mental Health (ACAMH; a non-profit organization) and Healthcare Convention for educational activity on attention-deficit hyperactivity disorder.

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