The Effectiveness of Metformin in Managing Second Generation Antipsychotic–Induced Weight Gain in Children and Adolescents

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Abstract

Objective: This study aimed to assess the effectiveness of metformin for antipsychotic-induced weight gain (AIWG) and determine whether the timing of metformin initiation and premorbid obesity moderated metformin effectiveness in children and adolescents on treatment with second-generation antipsychotics (SGAs).

Methods: A cohort of individuals 6 to 17 years of age, from 2016 to 2021, initiating a new SGA treatment and receiving a subsequent metformin prescription during SGA treatment were identified from the IQVIA Ambulatory EMR-US database. The changes in body mass index (BMI) *z* score before and after metformin initiation were assessed using the piecewise linear mixed-effects regression model.

Results: The results showed that the initiation of metformin was associated with a flattening out of the prior-metformin BMI *z* score trend. Relative to those who did not use metformin, metformin users had an additional monthly decrease in BMI *z* score of −0.053 (P=.0008) during the 6-month period after metformin initiation. Specifically, users who were non-obese before the intervention experienced a greater reduction in the BMI *z* score slope compared to those who were mildly-to-moderately obese and severely obese (non-obese – mildly-to-moderately obese: −0.07631, P=.0001; non-obese – severely obese: −0.09613, P<.0001). A different effect was not observed between patients who initiated metformin within versus beyond 90 days of SGA initiation. Extending the observation period to 12 months yielded comparable findings.

Conclusions: Adjuvant metformin helps manage AIWG in children and adolescents by flattening the upward AIWG trend rather than reversing it. The effect was more prominent before the development of obesity, suggesting that the early introduction of metformin for AIWG management may be warranted.

J Clin Psychiatry 2024;85(0):23m14894

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Pediatric patients appear to be particularly vulnerable to antipsychotic-induced weight gain (AIWG),[1] with up to 80% developing significant weight gain after starting an antipsychotic regimen.[1] Metformin is an antihyperglycemic agent used for decades for type 2 diabetes and has been associated with weight loss. The weight loss mechanism may involve reducing insulin resistance and suppressing appetite.[2]

The beneficial effect of metformin on AIWG in children and adolescents has been demonstrated in 4 randomized, placebo-controlled trials with sample sizes between 15 and 60 and follow-up periods up to 6 months.[3–6] These trials found that metformin reduced body mass index (BMI) *z* score significantly more than placebo, with an effect size ranging from −0.07 to −0.11. Although a randomized, placebo-controlled trial is the gold standard for establishing drug efficacy, the effectiveness of adjuvant metformin versus nonuse has yet to be evaluated in real-world practice.

A meta-analysis by de Silva et al[7] helped identify the optimal timing for adjuvant metformin initiation during second-generation antipsychotic (SGA) treatment. The meta-analysis evaluated SGA-naive adult patients who started metformin and an SGA concurrently and showed a much larger difference in mean body weight change (−5.94 kg [95% CI, −6.75 to −5.12 kg]) compared to trials of chronically medicated patients (−2.06 kg [95% CI, −2.71 to −1.41 kg]). However, a significant gap exists when translating the finding to AIWG management in pediatric practice. It remains unknown whether similar preventive effects also exist when adjuvant metformin is used in pediatric SGA recipients and whether the larger effect size observed in SGA-naive patients was because of their lack of prior

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Clinical Points

- Initiating metformin during second-generation antipsychotic (SGA) treatment can stop the increasing trend of antipsychotic-induced weight gain (AIWG) but may not be able to reverse it.
- To prevent AIWG, it is critical to initiate metformin before patients experience a significant weight gain.

SGA exposure or having less premorbid obesity compared to the chronic SGA users at metformin initiation.

Therefore, our study's objectives were to assess the effectiveness of adjuvant metformin on AIWG and determine whether the timing of metformin initiation and premorbid obesity status moderated metformin effectiveness in a large cohort of children and adolescents from a national electronic medical record (EMR) database.

METHODS

Data

IQVIA Ambulatory EMR is a collection of patient EMRs captured from interactions between a patient and their health care provider. Patient EMRs include a patient's demographics, problems, vital signs, laboratory test outcomes, diagnoses, procedures, and prescriptions. The dataset is sourced from over 800 ambulatory practices that cover more than 100,000 physicians. It includes over 82 million patients, with average history of 3 years, and some dating back to 2006.[8] The database is used in a variety of life sciences and commercial effectiveness studies. As a primary source or linked to other assets, IQVIA Ambulatory EMR-US is well-suited to connect patients' laboratory test outcomes/vital signs, health behaviors, and risk factors to clinical diagnosis and ordered therapies; enhance market sizing and other claims-based analytics by gleaning clinical insights; develop insights based on provider treatment decisions by indication and written prescription information; and identify hard-to-find populations with rare diseases not recognized by *ICD-9*/*ICD-10* codes.

Sample

This analysis comprised individuals 6 to 17 years of age, initiating a new SGA treatment, and receiving a minimum of 90 days of continuous SGA prescriptions from 2016 to 2021. A new treatment episode is defined as a new SGA prescription order after a 6-month active preceding period without an SGA prescription order.

Design

A piecewise linear mixed regression model was first applied to compare BMI *z* score change during the 6 months prior to and the 6 months after the initiation of adjuvant metformin between users and nonusers; then, the association of BMI *z* score change with the timing of metformin initiation (≤ 90 days vs > 90 days since SGA initiation) and baseline weight status (non-obese, mildly-to-moderately obese, and severely obese users) was further assessed among metformin users.

Comparing the BMI *z* Score Change Between Metformin Users and Nonusers

Adjuvant metformin users. Adjuvant metformin users were defined as patients who received a metformin prescription after the initiation of an SGA with at least a 1-week overlap between the SGA and metformin prescriptions. The date of metformin initiation is defined as the index date.

Adjuvant metformin nonusers. Each metformin user was matched with 4 individuals who continued SGA treatment but did not start metformin (nonusers). Matching is necessary because the chance of patients receiving adjuvant metformin is dependent on the duration of SGA exposure. Those with early SGA discontinuation were less likely to receive adjuvant metformin than the longer-term SGA users (immortal time bias). To preclude this bias associated with immortal person-time, which is common in studies comparing treatments against a nonuser comparator group, it is necessary to identify a specific time point among nonuse episodes to mark their study index date.[9,10] The 1-to-4 matching ratio is selected for the main analysis because it is a maximum matching ratio that allows each adjuvant metformin recipient to be matched with an equal number of unique nonusers (matching without a replacement).

Assessing the Association of BMI *z* Score Change With Premorbid Weight Status and the Timing for Metformin Initiation

Premorbid obesity. Metformin users were classified as being non-obese (BMI *z* score < 1.64 or BMI percentile < 95%), mildly-to-moderately obese (1.64 ≤ BMI *z* score < 2.32 or 95% ≤ BMI percentile < 99%), and severely obese (BMI *z* score ≥ 2.32 or BMI percentile ≥ 99%) based on the BMI measured closest to metformin initiation and taken within the 6-month period prior to metformin initiation. Body mass index (weight [kg]/height squared [m^2]) measurements were converted to age- and sex-specific BMI *z* scores and percentiles using the 2000 Centers for Disease Control and Prevention normative database.[11,12]

Timing for metformin initiation. Preventive use of adjuvant metformin was defined in clinical trials as starting SGA and metformin simultaneously,[13] while the trials that focused on the treatment of AIWG usually included patients who were stabilized on SGAs. However, the duration between SGA initiation and metformin initiation in real-world patients is a

continuous distribution (Supplementary Figure 1). Given both clinical trials and observational studies showed that the rapid weight increase associated with SGA happens during the acute phase of treatment (first 12 weeks),[14,15] we chose a 90-day cutoff since SGA initiation. We further defined patients who initiated metformin before the cutoff as early initiators and those who initiated metformin after the cutoff as late initiators.

Observation period. The weight change associated with adjuvant metformin was observed during the 6 months prior (baseline period) and the 6 months after the initiation of adjuvant metformin (index date) in the main analysis. Individual metformin recipients were followed until the discontinuation of SGA or adjuvant metformin or once they reached 6 months following the index date. The matched nonusers were followed until the discontinuation of SGA, the initiation of adjuvant metformin, or once they reached 6 months following the assigned index date. Treatment discontinuation was defined as the date either SGA or metformin was discontinued, indicated by either a noted removal by the physician or the date of the last prescription was prescribed.

Outcome measures. During the 6-month period prior to the index date and 6-month post-index period, all available BMI measures were considered in the analysis. Relative changes in the slope of BMI *z* score trajectory before and after metformin initiation were compared between the study groups.

Statistical Analysis

Visualization of individual- and group-level change in BMI z score before and after adjuvant metformin initiation. The individual-level BMI *z* score measured 6 months prior and 6 months after adjuvant metformin initiation was displayed using a spaghetti plot. The group-level BMI *z* score trajectories of the study cohort were visually presented using the locally weighted scatterplot smoothing (LOWESS) curve.[16,17]

Assessing the impact of adjuvant metformin on BMI z score trajectories using a piecewise linear mixed model. Changes in the slopes of BMI *z* score trajectories before and after adjuvant metformin initiation were modeled using piecewise linear mixed-effects regression with a breakpoint at metformin initiation time. Comparisons were made (1) between users and nonusers; (2) between users who were severely obese, mildly-to-moderately obese, and nonobese before metformin initiation; and (3) between early and late metformin initiators within each baseline weight category because of the existence of a significant interaction between patients' baseline weight status and the timing of metformin initiation (see Supplementary Table 2). A linear mixed model was selected to maximize the use of available BMI *z* measures while accounting for missing values.[18] In piecewise regression, also known as segmented regression, the independent variable (the initiation of adjuvant metformin) is partitioned into intervals and a separate line segment and fits each interval with a node connecting both segments.[19] The major strength of this analytic approach is its ability to distinguish the effect of the intervention from secular change, that is, change that would have happened even in the absence of the intervention. Estimating the intervention effect was done by comparing the slope of the outcome trajectory after the intervention to the slope of the trajectory during the pre-intervention period.

Propensity score adjustment for covariates. Since our group assignment was not randomized, we adjusted between-group differences using a propensity score. Two propensity scores were estimated: (1) for the propensity of receiving adjuvant metformin in all pediatric SGA recipients and (2) for the propensity of receiving adjuvant metformin among children in 3 prior-metformin weight categories.

Covariates included in propensity score estimation were collected during the 6-month period before the index date. These predictors include patient demographics (eg, age, sex, race), geographic region, baseline BMI *z* score (included only for the comparison between users and nonusers), family history of mental disorders, diagnoses, the index SGA, the index SGA prescriber specialty, the history of SGA switching, and comedications. To understand the independent effect of premorbid obesity and the duration between SGA and metformin initiation, each measure was included in the propensity score for the estimation of another.

Index SGA was defined as the individual SGA patients received on the index date. The history of SGA switching was defined as changing SGA during the 6-month pre-index period. The SGA switching was further categorized as switching from low risk to high risk, within the same risk, and switching from high risk to low risk according to the propensity of metabolic adverse effects associated with individual SGAs. The low-risk SGAs include aripiprazole, asenapine, ziprasidone, lurasidone, and cariprazine; the moderate-risk SGAs include risperidone, quetiapine, paliperidone, and iloperidone; and the high-risk agents include clozapine and olanzapine.[1]

Sensitivity Analysis

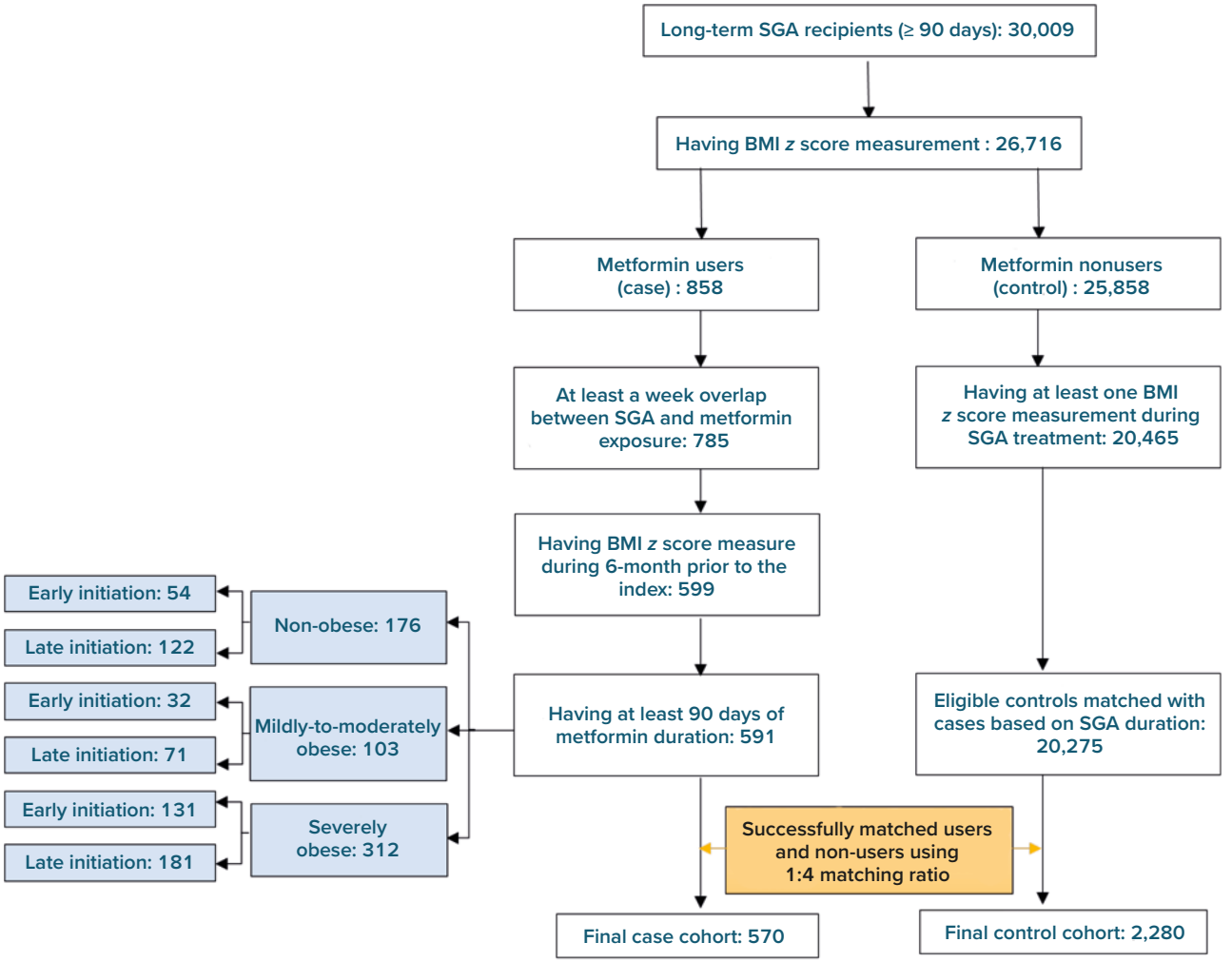
To test the robustness of the metformin effect on AIWG observed in the main analysis against extreme BMI *z* score change in a few patients (defined as having a BMI *z* score greater than 3 or less than −3), a sensitivity analysis was conducted after excluding these patients from the analysis.

A glossary table is included in Supplementary Table 3 to assist readers in understanding the terminology included in the Methods. Analyses were performed using SAS (version 9.4; SAS Institute Inc.; Cary, NC).

Ethics Statement

The study has been approved by the University of Houston Institutional Review Board (IRB).

Figure 1.
Schematic Diagram



Abbreviation: SGA = second-generation antipsychotic.

RESULTS

Study Cohort Characteristics

As presented in Figure 1, 591 adjuvant metformin recipients who met all inclusion criteria were identified, of whom 176 were classified as non-obese, 103 were mildly-to-moderately obese, and 312 were severely obese before the initiation of adjuvant metformin. Within each premorbid weight category, patients were further classified as early and late initiators according to the duration between SGA and metformin initiations.

The mean (SD) duration of metformin use was 365 days (365) and the median (interquartile range [IQR]) was 230 (98–493) days. The mean (SD) duration from SGA initiation to metformin initiation was 400 (462) days, with the median (IQR) being 221 (27.5–635) days. The social, demographic, and clinical characteristics of patients by study groups are available in Supplementary Tables 1 and 2.

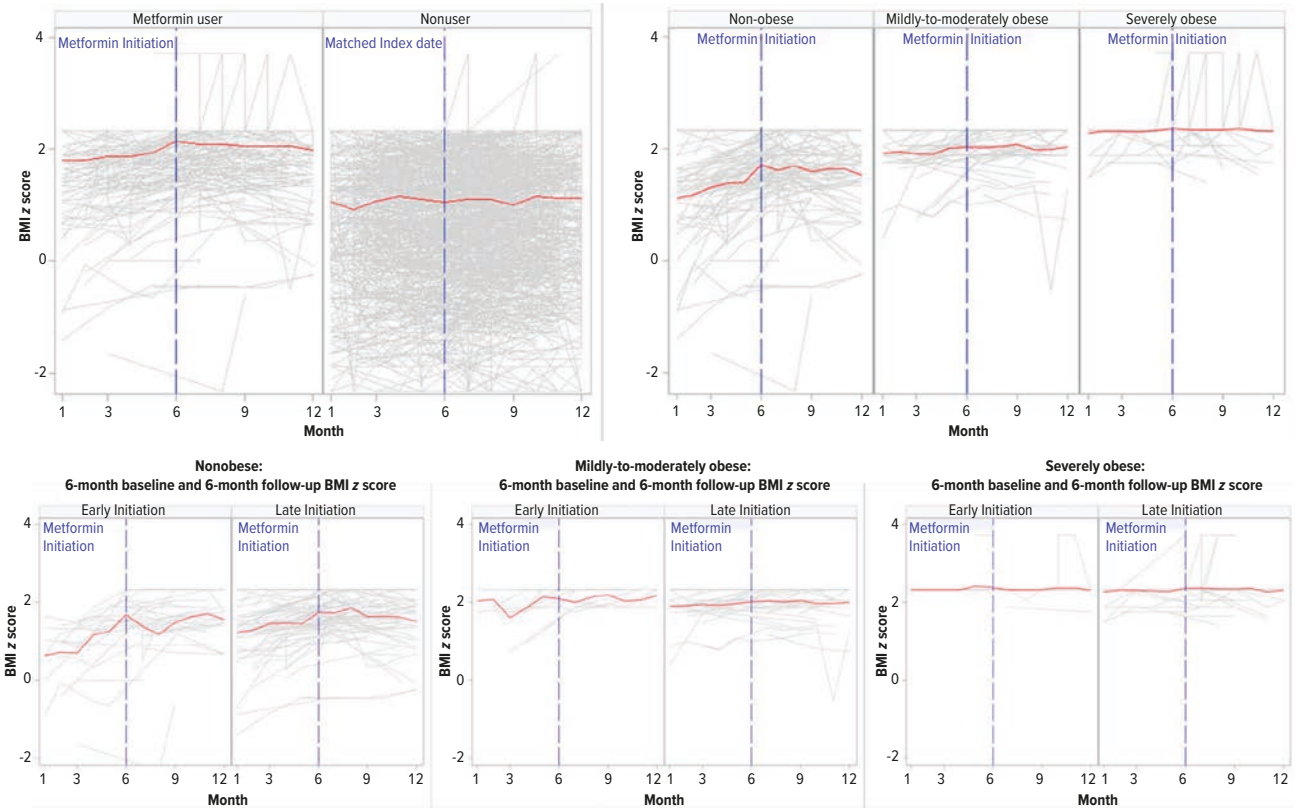
Change in BMI *z* Score Trajectory Associated With Adjuvant Metformin Initiation

Figure 2 presents the spaghetti plots with overlaid LOWESS curves of BMI *z* score 6 months before and 6 months after the metformin initiation. Tables 1 and 2 and Supplementary Figure 2 present the estimated change in BMI *z* score associated with adjuvant metformin use after propensity score adjustment.

The results show that all SGA recipients' BMI *z* score steadily increased during the pre-intervention period. The mean monthly increase of BMI *z* score in users was 0.0554 ($P < .0001$) in users and 0.0146 ($P = .0065$) in nonusers, which translates into clinically significant weight gain,

Figure 2.

Spaghetti Plots and LOWESS Curves of BMI *z* Score Trajectories Before and After the Initiation of Adjuvant Metformin



Abbreviations: BMI = body mass index, LOWESS = locally weighted scatterplot smoothing.

Table 1.

The Estimated Change in BMI *z* Score Associated With Adjuvant Metformin Initiation Between Users and Nonusers From the Linear Mixed-Effects Model

	BMI *z* Score Estimates								
								ΔPost-Index – Pre-Index	
	At Index	Pre-Index			Post-Index				
Group	Mean (SE)	Slope (SE)	95% CI	*P* Value	Slope (SE)	95% CI	*P* Value	Difference in Slopes (SE)	*P* Value
User	1.5835 (0.0069)	0.0554 (0.0086)	0.0385 to 0.0723	<.0001	0.0019 (0.0067)	−0.0112 to 0.015	.7751	−0.0535 (0.0132)	<.0001
Nonuser	0.9832 (0.0382)	0.0146 (0.0053)	0.0042 to 0.025	.0065	0.0137 (0.0041)	0.0057 to 0.0217	.0010	−0.0008 (0.0083)	.9169
User vs nonuser	…	…	…	…	…	…	…	−0.0527 (0.0156)	.0008
								Estimation (SE)	*P* Value
Propensity score for user and nonuser	…	…	…	…	…	…	…	0.2791 (0.1101)	.0113

[a]Index date for users: adjuvant metformin initiation date.
[b]Index date for nonusers: assigned index date.
Abbreviation: BMI = body mass index.

Table 2.

The Estimated Change in BMI *z* Score Associated With Adjuvant Metformin Initiation and Weight Status From Linear Mixed-Effects Model

	BMI *z* Score Estimates								
								ΔPost-Index – Pre Index	
	At Index	Pre-Index			Post-Index				
Weight Status	Mean (SE)	Slope (SE)	95% CI	*P* Value	Slope (SE)	95% CI	*P* Value	Difference in Slopes (SE)	*P* Value
Non-obese	0.8026 (0.0644)	0.1257 (0.0081)	0.1098 to 0.1416	<.0001	0.0034 (0.0061)	−0.0086 to 0.0154	.5838	−0.1223 (0.0123)	<.001
Early initiation	0.4472 (0.1376)	0.1526 (0.0206)	0.1122 to 0.193	<.0001	0.0327 (0.0138)	0.0057 to 0.0597	.0188	−0.1199 (0.0290)	<.001
Late initiation	0.9939 (0.0775)	0.1134 (0.0114)	0.0911 to 0.1357	<.0001	−0.0172 (0.0096)	−0.036 to 0.0016	.0757	−0.1306 (0.0187)	<.0001
Late initiation vs early initiation	…	…		…	…		…	−0.0107 (0.0345)	.7565
Mildly-to-moderately obese	1.7074 (0.0787)	0.0541 (0.0109)	0.0327 to 0.0755	<.0001	0.0081 (0.0081)	−0.0078 to 0.024	.3241	−0.0459 (0.0167)	.0060
Early initiation	1.4138 (0.1321)	0.0936 (0.0229)	0.0487 to 0.1385	<.0001	0.0364 (0.0153)	0.0064 to 0.0664	.0184	−0.0572 (0.0329)	.0831
Late initiation	1.8400 (0.0618)	0.0392 (0.0101)	0.0194 to 0.059	.0001	−0.0105 (0.0081)	−0.0264 to 0.0054	.1967	−0.0498 (0.0161)	.0022
Late initiation vs Early initiation	…	…		…	…		…	0.0074 (0.0367)	.8393
Severely obese	2.1827 (0.0503)	0.0248 (0.0074)	0.0103 to 0.0393	.0008	−0.0014 (0.0049)	−0.011 to 0.0082	.7835	−0.0262 (0.0104)	.0121
Early initiation	2.3345 (0.0651)	-0.0041 (0.0115)	−0.0266 to 0.0184	.7240	0.0018 (0.0005)	0.0008 to 0.0028	.7326	0.0058 (0.0141)	.6797
Late initiation	2.2720 (0.0273)	0.0171 (0.0005)	0.0161 to 0.0181	.0012	−0.0065 (0.0048)	−0.0159 to 0.0029	.1772	−0.0236 (0.0087)	.1772
Late initiation vs Early initiation	…	…	…	…	…	…	…	-0.0295	.0772
Non-obese vs mildly-to-moderately obese	…	…	…	…	…	…	…	−0.07631 (0.01993)	.0001
Non-obese vs severely obese	…	…	…	…	…	…	…	−0.09613 (0.01531)	<.0001
Mildly-to moderately obese vs severely obese	…	…	…	…	…	…	…	−0.01982 (0.01879)	.2918

	Estimation (SE)	*P* Value
Propensity score for non-obese, mild-to-moderately obese, and severely obese	0.1176 (0.0916)	.2000

defined as a 0.5-unit increase in BMI *z* score, in 10 months among users and 33 months among nonusers. After control of the BMI *z* score slope of nonusers, metformin initiation was associated with a significant reduction of the pre-metformin BMI *z* score slope in adjuvant metformin users (relative slope change after index date: users – nonusers: −0.0527, $P = .0008$). The reduction has neutralized the pre-metformin weight increase, and the slope of BMI *z* score trajectory turned flat in users after metformin initiation (slope [month] after index date: users: 0.0019, $P = .7751$). While the slope remained positive in the nonusers matched with users (slope [month] after index date: nonusers: 0.0137, $P = .001$).

Among metformin users, the mean monthly increase in BMI *z* score during the pre-intervention period also varied by patients' pre-metformin weight status. The change was most prominent among non-obese users (0.1257, $P < .0001$), followed by the mildly-to-moderately obese (0.0541, $P < .0001$) and severely obese users (0.0248, $P = .0008$). After metformin initiation, a larger relative BMI *z* score slope reduction was observed in non-obese users compared to those of mildly-to-moderately obese and severely obese users (relative slope change after index date: non-obese – mildly-to-moderately obese: −0.07631: $P = .0001$; non-obese – severely obese: −0.09613: $P < .0001$). The slope of BMI *z* score trajectory turned flat in all subgroups of the users classified based on premorbid obesity (slope [month] after index date: non-obese: −0.0034, $P = .5838$; mildly-to-moderately obese: 0.0081, $P = .3241$; severely obese: −0.0014, $P = .7835$).

The comparisons between early and late metformin initiators within each premorbid obesity category showed that the timing of metformin initiation did not affect the effect of metformin on BMI *z* score slope (relative slope change after index date: late initiation – early initiation: non-obese: −0.0107, $P = .7565$; mild-to-moderately obese: 0.0074, $P = .8393$; severely obese: −0.0236: $P = .0772$).

Sensitivity Analyses: 12-Month Change in BMI *z* Score Associated With Adjuvant Metformin Initiation

Substituting a 12-month follow-up period following the initiation of adjuvant metformin for the 6-month period did not alter the findings.

Sensitivity Analyses: Excluding the BMI *z* Score Outliers

BMI *z* score measures were greater than 3 or less than −3 for less than 1% of individuals (n = 15). In the non-obese subgroup, the monthly slope after the index date was −0.0015 ($P = .7828$). The mildly-to-moderately obese subgroup had a slope of −0.0001 ($P = .9971$), while the severely obese subgroup had a slope of −0.0024 ($P = .5892$). This suggested that the slope of the BMI *z* score trajectory remained flat across all subgroups, and there were no significant changes in the BMI *z* score after metformin initiation. This sensitivity analysis conducted on the subcohort excluding extreme BMI *z* scores yielded results similar to those of the main analysis, confirming the results' robustness and stability without the potential bias introduced by the extreme BMI *z* scores.

DISCUSSION

The study findings indicate that adjuvant metformin helps manage AIWG in children and adolescents by flattening the upward AIWG trend rather than reversing it. The BMI *z* score trajectories after metformin initiation were flat; regardless, the estimation was based on the entire adjuvant metformin cohort or based on the subgroups with various baseline weight status.

The subgroup analysis further showed that the effect was more prominent before the development of obesity.[3–6] There was a greater relative reduction in BMI *z* score among non-obese SGA recipients than among obese recipients during metformin treatment, and there was no difference in BMI *z* score reduction observed between mildly-to-moderately obese and severely obese individuals. However, the difference between study groups can be explained mainly by the steeper prior-metformin slope of non-obese metformin users relative to their obese counterparts. Given that more than 70% of the adjuvant metformin users are obese, and more than 50% were severely obese at the time of metformin initiation, the finding implies that adjuvant metformin should probably be considered for non-obese SGA users to prevent the development of SGA-induced obesity.

The clinical trial results suggested that the preventive use of metformin, defined as concurrently initiating SGA and metformin, was associated with significantly more BMI *z* score reduction than the use in chronic SGA users who have experienced significant weight gain.[3–6] However, our subgroup analysis did not find a difference in BMI *z* score reduction between the users who initiated metformin within the first 12 weeks of SGA treatment and those who initiated metformin later. A result favoring the early metformin initiators was not observed in our study, probably because earlier and later metformin initiators as defined in our study are different from the categories as defined in clinical trials. In fact, preventive use as defined in clinical trials is rare in real-world practice, probably because using a medication to address the side effect of another has not been well accepted in pediatric practice.

This study is the first to examine the effectiveness of adjuvant metformin in children and adolescents with AIWG and also the first to assess the moderating effect of weight status and assess the timing of medication initiation relative to metformin effectiveness. However, despite its strengths, our study has some limitations. The relatively small sample size prohibits examining whether metformin dose moderated treatment effectiveness. This analysis, based on electronic medical records, could not confirm treatment adherence to SGAs or metformin. We also did not consider SGA dose as a covariate in the analysis; some evidence suggests that AIWG is dose dependent.[20,21] Further studies are needed to answer whether stabilizing AIWG improves SGA medication adherence and treatment outcomes, to understand the barriers to prescribing adjuvant metformin for pediatric patients on SGAs, and to determine whether AIWG could be prevented by initiating the treatment using new SGAs, which may not cause weight gain.

CONCLUSIONS

Metformin is an effective intervention for AIWG in children and adolescents. It helps manage AIWG through flattening out the upward AIWG trend rather than reversing it. Therefore, adjuvant metformin should be considered to minimize further weight gain in obese pediatric patients on SGAs and in those who are at risk, in order to prevent SGA-induced overweight and obesity.

Article Information

Published Online: Month 00, 2023. https://doi.org/10.4088/JCP.23m14894

Submitted: April 4, 2023; accepted November 2, 2023.

To Cite: Chen H, Lyu N, Calarge C, et al. The effectiveness of metformin in managing second generation antipsychotic–induced weight gain in children and adolescents. *J Clin Psychiatry.* 2024;85(0):23m14894.

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Relevant Financial Relationships: The authors report no financial or other relationship relevant to the subject of this article.

Funding/Support: This study was funded by the National Institute of Mental Health (NIMH; project number R21MH125039-01).

Role of the Funders/Sponsors: The supporters had no role in the design, analysis, interpretation, or publication of this study.

Supplementary Material: Available at Psychiatrist.com.

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