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Longitudinal impact of different treatment sequences of second-generation antipsychotics on metabolic outcomes: a study using targeted maximum likelihood estimation

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Original Article

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Abstract

Background. Second-generation antipsychotics (SGAs) cause metabolic side effects. However, patients' metabolic profiles were influenced by time-invariant and time-varying confounders. Real-world evidence on the long-term, dynamic effects of SGAs (e.g. different treatment sequences) are limited. We employed advanced causal inference methods to evaluate the metabolic impact of SGAs in a naturalistic cohort.

Methods. We followed 696 Chinese patients with schizophrenia-spectrum disorders receiving SGAs. Longitudinal targeted maximum likelihood estimation (LTMLE) was used to estimate the average treatment effects (ATEs) of continuous SGA treatment versus 'no treatment' on metabolic outcomes, including total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglyceride (TG), fasting glucose (FG), and body mass index (BMI), over 6–18 months at 3-month intervals. LTMLE accounted for time-invariant and time-varying confounders. Post-SGA discontinuation side effects were also assessed.

Results. The ATEs of continuous SGA treatment on BMI and TG showed an inverted U-shaped pattern, peaking at 12 months and declining afterwards. Similar patterns were observed for TC and LDL, albeit the ATEs peaked at 15 months. For FG and HDL, the ATEs peaked at ~6 months. The adverse impact of SGAs on BMI persisted even after medication discontinuation, yet other metabolic parameters did not show such lingering side effects. Clozapine and olanzapine exhibited greater metabolic side effects compared to other SGAs.

Conclusions. Our real-world study suggests that metabolic side effects may stabilize with prolonged continuous treatment. Clozapine and olanzapine confer higher cardiometabolic risks than other SGAs. The side effects of SGAs on BMI may persist after drug discontinuation. These insights may guide antipsychotic choice and improve management of metabolic side effects.

Introduction

Second-generation antipsychotics (SGAs), while preferred over first-generation drugs for better tolerability, are known to cause metabolic side effects, including weight gain, dyslipidemia, and hyperglycemia, requiring regular monitoring (Bernardo et al., 2021; Chaplin & Taylor, 2014; Divac, Prostran, Jakovcevski, & Cerovac, 2014; Hirsch et al., 2018; Kurzthaler & Fleischhacker, 2001).

Comparative studies of SGAs showed that olanzapine and clozapine have the worst metabolic profiles, while aripiprazole, brexpiprazole, cariprazine, lurasidone, and ziprasidone have better outcomes. However, most studies are short-term, highlighting the need for longer-term real-world research (Burschinski et al., 2023; Pillinger et al., 2020; Rummel-Kluge et al., 2010).

Patients with schizophrenia and psychotic disorders usually receive long-term antipsychotic treatments, and clinicians may consider phase-specific care to address patients' changing needs

throughout the illness (e.g. the use of 'minimum effective dose' of SGAs for stabilized remitted patients). Given that the efficacy, preparations, and side effects of SGAs differ considerably, 'switching' between different antipsychotics is also common when patients develop extrapyramidal, metabolic, or other side effects, treatment nonresponse, or problems in treatment adherence (Buckley & Correll, 2008). This highlights the *dynamic* nature of antipsychotic prescriptions in psychosis, which was very seldom investigated in previous studies.

Additionally, metabolic agents like metformin and simvastatin are commonly prescribed for SGAs' metabolic side effects, potentially acting as time-varying confounders in observational studies. Recent evidence (Cipriani, Boso, & Barbui, 2009) suggests these effects vary based on combinations with other psychotropic medications, prior side effects, and current metabolic profiles. While Randomized controlled trials (RCTs) provide robust designs, they often fail to account for these dynamic, time-varying factors. The recent network meta-analyses (Pillinger et al., 2020) of RCT data (Burschinski et al., 2023) could not adequately address the complexities of switching between SGAs and their cumulative effects on metabolic profiles. Moreover, RCTs struggle to study how different *sequences* of treatments, which can vary over time, affect the severity of side effects. Also, previous studies (Pillinger et al., 2020) typically involved short follow-up periods (e.g. 6 weeks), and many predominantly recruited Caucasians (Burschinski et al., 2023), despite that non-Caucasian patients may exhibit different metabolic responses (DeBoer, 2011). It is, therefore, necessary to examine naturalistic and observational data in a cohort of patients, who received SGAs for a longer term (preferably in non-Caucasian populations) to capture these real-world complexities (Meyer et al., 2009).

When estimating the causal effects of SGAs on metabolic side effects, it is essential to account for time-varying confounders, including metabolic medications and SGA prescription sequences. Conventional analytical methods (Robins, Hernan, & Brumback, 2000), such as time-dependent Cox regression and generalized estimating equations, can yield biased estimates in the presence of these confounders (Hernán, Brumback, & Robins, 2000). Addressing time-varying confounding requires more sophisticated statistical methodologies (Schuler & Rose, 2017).

Targeted maximum likelihood estimation (TMLE) (Schuler & Rose, 2017) is a doubly robust method for estimating causal effects. Longitudinal TMLE (LTMLE) (Schomaker, Luque-Fernandez, Leroy, & Davies, 2019) extends the principles of the TMLE to accommodate the complexities inherent in longitudinal studies, including time-varying treatments and confounders. Specifically, the LTMLE framework has the following advantages for studying the metabolic side effects of SGAs:

1. First, the framework can account for ***time-varying treatment***, which other methods often cannot. We aim to study how ***dynamic treatment sequences***, changing over time, affect metabolic parameters. For example, a subject may be treated continuously (1,1,1), only at the first time point (1,0,0), or at the first two time-points (1,1,0). Previous studies on metabolic side effects of SGAs have focused only on cross-sectional treatment status, not the full treatment sequence.
2. LTMLE can also handle ***time-varying confounders/covariates***, such as concomitant drugs. LTMLE is considered an established method for causal inference in longitudinal studies due to its ability to tackle complex confounding patterns. Other commonly used methods, such as linear mixed models (Shardell & Ferrucci, 2018), cannot readily handle time-varying covariates.
3. LTMLE is considered ***'doubly robust'*** because it yields consistent estimates as long as either the outcome model or the treatment mechanism is correctly specified, even if the other model is mis-specified. This robustness to misspecification is a key strength of LTMLE. Here, the outcome model refers to the statistical framework that predicts expected outcomes based on measured covariates. In our study, this model estimates how metabolic outcomes are influenced by different sequences of SGAs. The treatment mechanism represents the process determining treatment assignment over time. It captures how clinicians' decisions about subsequent treatments are influenced by patient characteristics and previous treatment responses.

Given the above advantages, we employed the LTMLE framework (Lendle, Schwab, Petersen, & van der Laan, 2017) to investigate the joint treatment effects of different SGA treatment sequences on metabolic profiles, including total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides (TG), fasting glucose (FG), and body mass index (BMI).

In summary, this study aims to (1) investigate the side effects of SGAs under continuous treatment for varying durations (6, 9, 12, 15, and 18 months), compared to no treatment throughout the same follow-up period; (2) evaluate whether the side effects of SGAs on metabolic parameters persist after discontinuation. To address this question, we compared metabolic outcomes at 12 months for SGAs taken for varying durations versus no treatment all along; and (3) quantify the causal effects of SGAs on metabolic outcomes, accounting for time-varying confounding. We also assessed whether clozapine and olanzapine were causally linked to more severe metabolic side effects than other SGAs.

Overall, our approach allows for a comprehensive assessment of the long-term metabolic effects of SGAs in real-world settings, accounting for the complexities of treatment patterns and time-varying confounders.

Methods

Our sample

We recruited 768 patients with schizophrenia spectrum disorders attending the outpatient clinic at Castle Peak Hospital in Hong Kong during the recruitment period 2009–2021. Inclusion criteria were (1) Han Chinese ethnicity, (2) age 18 or older, (3) diagnosis of schizophrenia or schizoaffective disorder according to ICD-10 (Fung, Xu, & Bodenreider, 2020), (4) metabolic outcome measures available at three or more time points, and (5) at least three outcome measures at a single time point. Exclusion criteria included (1) a history of metabolic disorders (e.g. diabetes, dyslipidemia) before SGA treatment and (2) lack of psychiatric follow-up as of March 2021. We retrieved electronic health records to gather detailed prescription history and metabolic outcomes. In our analysis, the first prescription date was designated time 0, which refers to the baseline. More specifically, baseline was defined as the time point when each patient had first medication record during the study period, regardless of the duration of illness prior to this point. Ultimately, after further filtering and data cleaning, 696 patients were included, aged 19 to 73, with 54% female. Further baseline characteristics are detailed in Supplementary Table S7.

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Outcome variables

We assessed six metabolic indicators: TC, HDL, LDL, TG, FG, and BMI. Given the naturalistic nature of the cohort, metabolic profiles were measured at varying time points (Hu, 2021) (unbalanced dataset). We utilized linear mixed models (Gałecki, Burzykowski, Gałecki, & Burzykowski, 2013) to impute values of metabolic parameters at pre-specified time points (Fung, Xu, & Bodenreider, 2020). More specifically, we implemented a structured imputation framework based on our 18-month follow-up: (1) For the main analysis, data were imputed at 3-month intervals, resulting in six time points per patient; (2) For sensitivity analysis, data were imputed at 1-month intervals, yielding 18 time points per patient.

Our imputation model included prescribed drugs, treatment durations, and patient demographics (age, sex, and education) as predictors. Records were grouped by patient ID to account for random intercepts and slopes (Appendix A). In addition to single imputation, we also employed multiple imputation (five iterations) to account for uncertainty in the imputed values; results were pooled using the Rubin's rule (Rubin, 2004).

Exposure variables

Exposure variables represented the use of various SGAs, including *clozapine, olanzapine, amisulpride, paliperidone, risperidone, quetiapine*, and *lurasidone* (Supplementary Table S1). We coded exposure as a binary indicator, marking 1 if a subject used any SGA at a specific time point and 0 if not. For example, if a subject received any of these SGAs at time t, the exposure variable A_t was coded as 1; otherwise, it was coded as 0. Aripiprazole was excluded from the primary analysis because previous studies indicate that it is generally not associated with adverse metabolic outcomes (Jerrell, McIntyre, & Tripathi, 2010) but included in sensitivity analyses for robustness evaluation.

Confounding variables

We included both time-invariant and time-varying confounders in our analysis. Baseline confounders consisted of patients' age, sex, and metabolic measures at t_0. Time-varying confounders included drugs like metformin, atorvastatin, simvastatin, and valproate (Supplementary Table S1). Metformin, atorvastatin, and simvastatin lower glucose, lipids, and weight, while valproate (taken by 82 patients) is linked to weight gain and metabolic abnormalities (Belcastro, D'Egidio, Striano, & Verrotti, 2013; Shnayder et al., 2023). SGA prescription status was also treated as a time-varying covariate. Additionally, we included the mean age of each subject over the follow-up as a time-invariant confounder.

The LTMLE model, by default, includes all 'parent nodes' from preceding time points as predictors for the dependent variables (Appendix B). 'Parent nodes' refer to the covariates, exposures, and outcomes from *earlier time-points* used to model the outcome at a given time-point. This approach accounts for time-varying confounding and dynamic treatment effects. Figure 1A provides an illustration. For example, the outcome (Y_3) at the 3rd time point (t_3) was modeled based on all the covariates/confounders (L), treatments (A), and outcomes (Y) at *all previous time-points* (t_0, t_1, t_2). Including this comprehensive set of covariates ensures proper

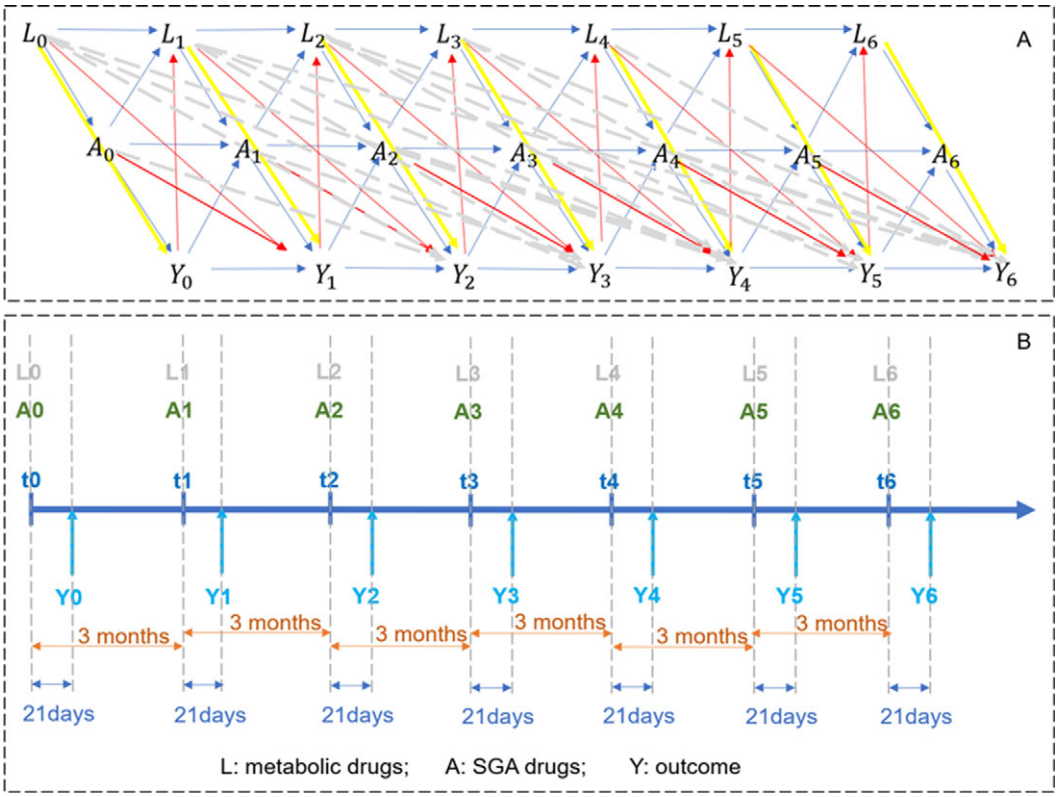

Figure. 1. Assumed directed acyclic graph (A) and the sequential relationships among exposure (B), with the outcome and time-varying confounders at different time-points. L: Time-varying confounders; A: Treatment at each time-point; Y: Outcome at each time-point.

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control for time-varying confounding variables and provides a robust estimate of causal effects.

Statistical analysis using LTMLE

We employed LTMLE (Lendle, Schwab, Petersen, & van der Laan, 2017) to analyze the joint effects of SGAs on metabolic indicators compared to non-SGA users. As mentioned earlier, LTMLE is a doubly robust method for estimating causal effects (Van Der Laan & Rubin, 2006), integrating an outcome model and a propensity score (PS)-based treatment model to minimize bias from potential model misspecification. This methodology is considered 'doubly robust' because it yields consistent estimates as long as either the outcome model or the treatment mechanism is correctly specified, even if the other model is misspecified. Details can be found in Appendix C.

To address multiple testing, we employed both the Bonferroni and the Benjamini-Hochberg (BH) false discovery rate (FDR) approach.

Estimating the joint effect of treatment

Using the LTMLE framework, we estimated the metabolic effects of taking SGAs during the follow-up period, by comparing the metabolic profiles of patients treated with SGAs to those never treated with SGAs. Specifically, we estimated the ***average treatment effects*** (ATEs) of SGAs on metabolic parameters by comparing two scenarios, Situation A ('what if SGAs were taken throughout the follow-up period') versus Situation B ('what if no SGAs were taken during the follow-up period'). Situation B encompasses the use of any non-SGA drugs (including, for example, first-generation antipsychotics) or no medications at all. Additionally, we compared the ATEs of clozapine and olanzapine to the ATEs of other SGAs. Details of ATE estimation can be found in Appendix D.

We based our analyses on a counterfactual framework, with the network structure shown in Figure 1A. In this framework, L represents time-varying confounders, A is the exposure (SGAs), and Y is the outcome, with time-points indicated. To adjust for the impact of metabolic outcomes on SGA prescriptions, we included intermediate Y variables (Figure 1A). Time 0 (t_0) was defined by the first medication record for each patient, with a 3-month interval between time points.

L_t and A_t were defined at each time-point t, while Y_t was recorded 21 days later to account for delayed metabolic side effects, based on goodness-of-fit testing from our previous study (Wong et al., 2024). Figure 1B shows the sequential relationships between exposure, outcome, and time-varying confounders. Analyses were conducted using the R package 'ltmle' (Lendle, Schwab, Petersen, & van der Laan, 2017) (version_1.2.0).

Sensitivity analyses

Several sensitivity analyses were conducted to test the robustness of our findings. *First*, we excluded intermediate outcomes from the model, comparing results with and without this adjustment. *Second*, we adjusted the time intervals (1 and 3 months) while maintaining the same total follow-up duration. *Third*, although studies have generally shown that aripiprazole seldom causes metabolic side effects (Pillinger et al., 2020), we included this SGA in sensitivity analysis to validate our findings. *Fourth*, we addressed the possibility that patients might discontinue SGAs during follow-up by implementing an alternative exposure definition. Specifically, we defined exposure based on the percentage of time receiving SGAs during the observed time interval (i.e. interval-based). We set different cut-off values to determine whether exposure at time t is coded as 1 or 0. For example, if cut-off = 0.5, we coded the exposure at time t as 1 if the patient received SGAs for >50% of the time in the interval (t, t+1) (Supplementary Table S2). *Finally*, to further evaluate clinical relevance of our results, we dichotomized the continuous metabolic parameters to compare the odds of abnormal outcomes between the 'if always treated' versus 'if never treated' scenarios (see Supplementary Text).

Results

Continuous SGA treatment vs no treatment (for different follow-up periods)

We first compared 'what if all the participants were always treated during the follow-up period' versus 'what if all the participants were never treated'. The results are shown in Figure 1B and Table 1. We studied the effects of continuous SGA treatment at 6, 9, 12, 15, and 18 months.

Overall, for BMI and TG, ATEs initially increased and then decreased over time, when comparing 'always-treated' to 'never-treated'. A quadratic fit showed ATEs peaked at around 12 months for BMI and TG, and 15 months for TC and LDL. HDL fluctuated but increased from 6 to 18 months.

Specifically, the ATE for BMI was 0.707 kg/m² (95% CI = 0.564–0.851) at 6 months, increasing to 0.811 kg/m² (95% CI = 0.63–0.991) at 12 months, and decreasing to 0.623 kg/m² (95% CI = 0.389–0.857) at 18 months. TG showed a similar pattern, with ATE increasing from 0.195 mmol/L (95% CI = 0.128–0.262) at 6 months to 0.241 mmol/L (95% CI = 0.155–0.328) at 12 months, then decreasing to 0.169 mmol/L (95% CI = 0.064–0.274) at 18 months. For TC and LDL, ATEs peaked at 15 months. The ATE for TC increased from 0.109 (95% CI = 0.038–0.179) mmol/L at 6 months to 0.153 (95% CI = 0.069–0.237) mmol/L at 15 months, and then decreased to 0.094 (95% CI = −0.026–0.214) mmol/L at 18 months. The ATE for LDL increased from 0.095 (95% CI = 0.037–0.154) at 6 months to 0.125 (95% CI = 0.054–0.196) mmol/L at 15 months. HDL showed no clear pattern, with slight fluctuations of ATEs over time. The most negative ATE for HDL occurred at 6 months, but it increased slightly from 6 to 15 months. For FG, the highest ATE was observed at 6 months, followed by a decreasing trend.

Sensitivity analysis with a 1-month interval

We conducted sensitivity analysis with 1-month follow-up intervals, evaluating ATEs from the 4th month onward. As shown in Figure 2, at 3-month intervals, the ATEs of most metabolic outcomes initially increased but then decreased. With 1-month intervals and the same follow-up periods, BMI, TG, TC, FG, and LDL showed similar patterns (Supplementary Figure S1), indicating that the observed trends were likely robust. The trends before 6 months are not captured in Figure 2 but can be observed in Supplementary Figure S1.

Notably, for FG, the ATEs peaked at 4 months and then gradually decreased until 12 months, with a slightly increasing trend between 12 and 18 months (Supplementary Figure S1). The ATEs for HDL decreased between 4 and 6 months, followed by a

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Table 1. Average treatment effect (ATE) between 'always treated by SGAs' and 'never treated by SGAs' (with adjustment of intermediate outcomes)

Outcome	ATE	std.dev	CI_0.025	CI_0.975	Follow_up_length	P_value	P_adjust_bonferroni	P_adjust_fdr
FG	0.148	0.036	0.079	0.218	6 months	3.13E–05	9.39E–04	7.22E–05
	0.128	0.036	0.057	0.198	9 months	3.64E–04	1.09E–02	6.42E–04
	0.09	0.04	0.012	0.169	12 months	2.35E–02	7.05E–01	2.52E–02
	0.105	0.034	0.039	0.171	15 months	1.84E–03	5.52E–02	2.63E–03
	0.097	0.04	0.018	0.176	18 months	1.66E–02	4.98E–01	1.84E–02
BMI	0.707	0.073	0.564	0.851	6 months	5.22E–22	1.57E–20	1.04E–20
	0.694	0.072	0.553	0.836	9 months	6.91E–22	2.07E–20	1.04E–20
	0.811	0.092	0.63	0.991	12 months	1.41E–18	4.23E–17	1.41E–17
	0.758	0.102	0.557	0.958	15 months	1.28E–13	3.84E–12	9.60E–13
	0.623	0.119	0.389	0.857	18 months	1.82E–07	5.46E–06	5.46E–07
TC	0.109	0.036	0.038	0.179	6 months	2.57E–03	7.71E–02	3.42E–03
	0.13	0.044	0.043	0.216	9 months	3.28E–03	9.84E–02	4.10E–03
	0.146	0.05	0.048	0.244	12 months	3.61E–03	1.08E–01	4.17E–03
	0.153	0.043	0.069	0.237	15 months	3.62E–04	1.09E–02	6.42E–04
	0.094	0.061	−0.026	0.214	18 months	1.24E–01	1.00E+00	1.24E–01
HDL	−0.035	0.006	−0.047	−0.023	6 months	8.85E–09	2.66E–07	4.43E–08
	−0.031	0.006	−0.042	−0.019	9 months	3.07E–07	9.21E–06	7.68E–07
	−0.032	0.006	−0.044	−0.02	12 months	2.33E–07	6.99E–06	6.35E–07
	−0.028	0.007	−0.042	−0.014	15 months	7.45E–05	2.24E–03	1.60E–04
	−0.03	0.008	−0.045	−0.014	18 months	2.51E–04	7.53E–03	5.02E–04
LDL	0.095	0.03	0.037	0.154	6 months	1.37E–03	4.11E–02	2.16E–03
	0.111	0.038	0.037	0.185	9 months	3.43E–03	1.03E–01	4.12E–03
	0.121	0.04	0.042	0.2	12 months	2.62E–03	7.86E–02	3.42E–03
	0.125	0.036	0.054	0.196	15 months	5.62E–04	1.69E–02	9.37E–04
	0.093	0.046	0.002	0.183	18 months	4.41E–02	1.00E+00	4.56E–02
Triglycerides	0.195	0.034	0.128	0.262	6 months	1.32E–08	3.96E–07	5.66E–08
	0.21	0.038	0.136	0.285	9 months	3.11E–08	9.33E–07	1.17E–07
	0.241	0.044	0.155	0.328	12 months	4.82E–08	1.45E–06	1.61E–07
	0.225	0.038	0.151	0.3	15 months	2.77E–09	8.31E–08	1.66E–08
	0.169	0.053	0.064	0.274	18 months	1.57E–03	4.71E–02	2.36E–03

1) The interval between each time point was 3 months.
2) The definition of treatment (7 SGAs): taking any of these SGAs, including clozapine, olanzapine, amisulpride, paliperidone, risperidone, quetiapine, or lurasidone; the definition of time-varying confounders (4 drugs): taking any of these drugs, including metformin, atorvastatin, simvastatin, or valproate.
3) Treatment is coded as 1 if the patient took SGAs at the time-point, otherwise 0.
4) Abbreviation: TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; FG, fasting blood glucose level; BMI, body mass index; std.dev: Standard deviation.
5) Both Bonferroni correction and Benjamini-Hochberg (BH) false discovery rate (FDR) correction were used. Each table represents a distinct set of analyses with its own hypothesis tests. We set an FDR threshold of 0.1 in this study.

relatively steady (but slightly increasing) trend from 6 to 18 months. These findings suggested that the side effects of SGAs on HDL levels were the most pronounced at around 6 months after continuous treatment.

Alternative 'interval-based' treatment definitions

Using alternative interval-based treatment definitions, we observed similar patterns with smaller ATEs (Supplementary Table S5). For instance, at 18 months, the ATE for BMI was 0.623 kg/m^2 (95% CI = 0.389–0.857) when defining the treatment as 'patients taking SGAs at the specified time points', compared to 0.357 kg/m^2 (95% CI = 0.136–0.579) when defining the treatment as 'patients taking SGAs more than 80% of the time in the observed interval'.

Clozapine and olanzapine versus other SGAs

Given that clozapine and olanzapine are associated with more serious metabolic side effects in previous studies[8], we stratified patients who started with SGAs and compared their differences between two counterfactual scenarios, Situation A' ('what if clozapine or olanzapine was taken throughout the follow-up') and Situation B' ('what if other SGAs were taken throughout the follow-up').

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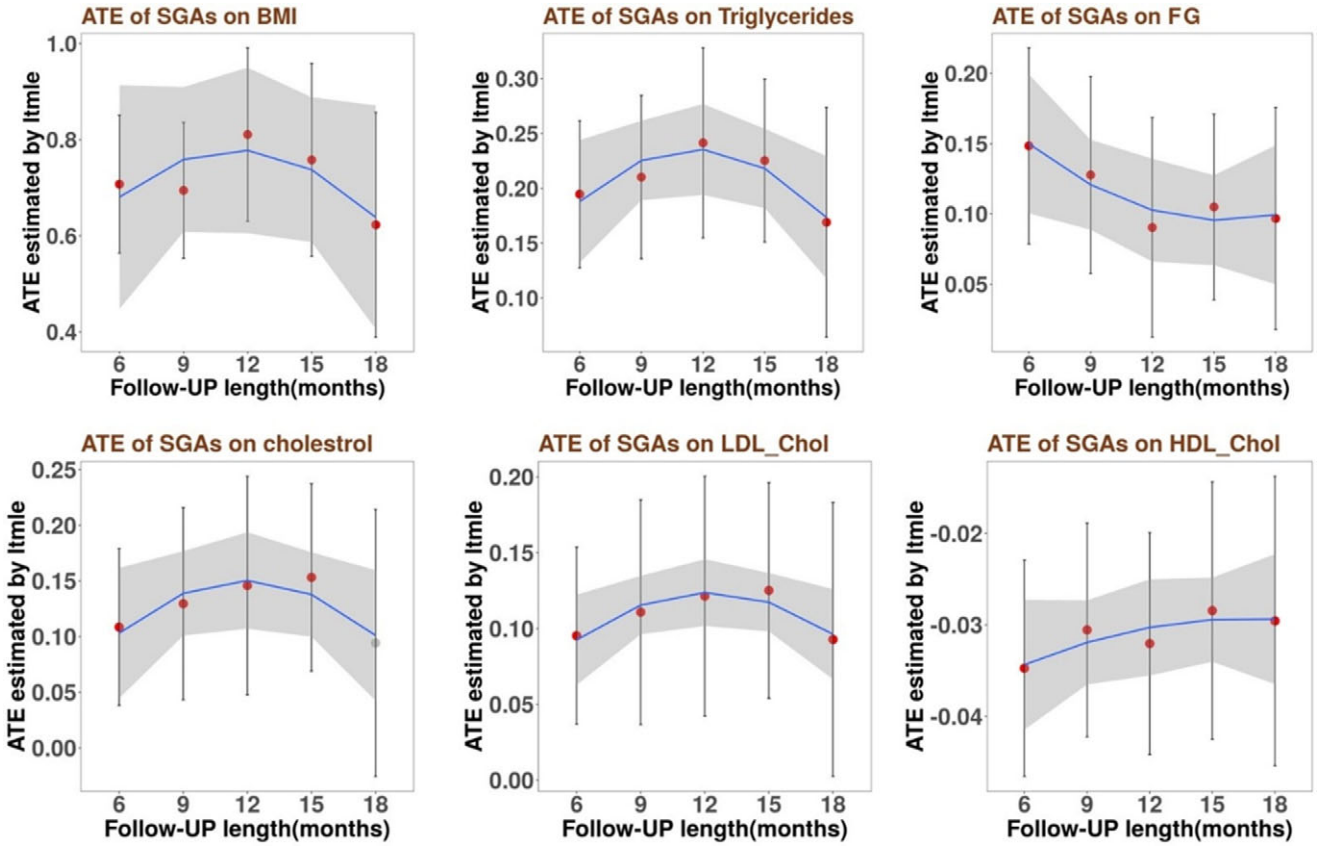

Figure 2. Average treatment effects (ATEs) of six outcomes for different FU lengths based on a 3-month interval.
The red data points indicate a statistically significant difference ($p < 0.05$) in the outcome measure between 'always being treated' and 'never being treated' groups, whereas the gray data points represent nonsignificant differences.
The blue line is generated on the basis of 'ATE ~ follow-up lengths + square (follow-up lengths)', and the gray area indicates the 95% confidence interval.
Abbreviations: TC, 'total cholesterol'; HDL, 'high-density lipoprotein'; LDL, 'low-density lipoprotein'; FG, 'fasting blood glucose level'; BMI, 'body mass index'; FU, 'Follow-up'.

We found a positive ATE for BMI of 0.947 kg/m² (95% CI = 0.461–1.433) at 18 months (Table 2), indicating a greater increase in BMI among patients treated with clozapine or olanzapine. Positive ATEs were also observed for FG, TC, LDL, and TG, with ATEs of 0.178 (95% CI = 0.067–0.29) mmol/L, 0.283 (95% CI = 0.118–0.447) mmol/L, 0.205 (95% CI = 0.083–0.327) mmol/L, and 0.36 (95% CI = 0.238–0.481) mmol/L, respectively. Conversely, HDL showed a negative ATE of −0.064 mmol/L (95% CI = −0.099–0.029), suggesting lower HDL levels in those treated with clozapine or olanzapine.

Metabolic outcomes at 12 months with different durations of SGA treatment

We also compared metabolic outcomes at 12 months, comparing 'SGAs taken for varying durations (3, 6, 9, and 12 months)' versus 'no treatment all along' (see Table 3 and Supplementary Figure S2).

Interestingly, our findings suggested lingering side effects of SGA treatment on BMI. Regardless of the treatment duration, BMI remained significantly higher at 12 months compared to 'no treatment', even after SGA discontinuation. However, this effect was not seen for other metabolic outcomes, where the effect sizes were non-significant if the drug had been discontinued for at least 3 months before the final assessment.

As an alternative approach to analyzing the cumulative effects of SGAs, we also compared SGAs taken for different durations to continuous SGA treatment throughout the follow-up period (Supplementary Table S4). If the SGA side effects do not persist after discontinuation, we would expect metabolic outcomes for shorter SGA treatment durations to be significantly better than those under continuous SGA treatment. As shown in Supplementary Table S4, we observed such patterns for almost all the metabolic outcomes.

With respect to BMI, we found that SGA discontinuation before the end of follow-up was associated with a significantly lower BMI than continued SGA treatment. In our previous analysis, we observed that BMI remained elevated despite discontinuation, but this was in comparison to those never treated with SGAs. Taken together, the findings suggest that for those who take SGAs for a limited duration during FU, their BMI might fall between those never treated with SGAs and those who receive continuous SGA treatment.

Additional sensitivity analyses

First, we conducted a sensitivity analysis with a 1-month follow-up interval, as detailed above. Second, we compared the results with and without adjustment for intermediate metabolic outcome values (Table 1 and Supplementary Table S3). After the above sensitivity analyses, we observed similar patterns of results. Third, when including aripiprazole as an SGA, the results remained similar,

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Table 2. Average treatment effect (ATE) between patients treated with clozapine or olanzapine and those treated by *other* SGAs throughout the follow-up period (with adjustment for intermediate outcomes)

Outcome	ATE	std. dev	CI_0.025	CI_0.975	Follow_up_ length	Treatment_Comparison	P_value	P_adjust_ bonferroni	P_adjust_fdr
FG	0.185	0.039	0.109	0.26	6 months	'If always treated' versus 'If never treated'	1.72E–06	5.16E–05	1.03E–05
	0.152	0.044	0.066	0.238	9 months	'If always treated' versus 'If never treated'	5.11E–04	1.53E–02	8.07E–04
	0.146	0.062	0.025	0.267	12 months	'If always treated' versus 'If never treated'	1.78E–02	5.34E–01	1.92E–02
	0.191	0.052	0.089	0.293	15 months	'If always treated' versus 'If never treated'	2.32E–04	6.96E–03	4.09E–04
	0.178	0.057	0.067	0.29	18 months	'If always treated' versus 'If never treated'	1.70E–03	5.10E–02	2.32E–03
BMI	0.789	0.169	0.458	1.121	6 months	'If always treated' versus 'If never treated'	3.10E–06	9.30E–05	1.33E–05
	0.654	0.231	0.201	1.107	9 months	'If always treated' versus 'If never treated'	4.66E–03	1.40E–01	6.08E–03
	0.903	0.198	0.516	1.291	12 months	'If always treated' versus 'If never treated'	4.89E–06	1.47E–04	1.82E–05
	1.006	0.235	0.547	1.466	15 months	'If always treated' versus 'If never treated'	1.79E–05	5.37E–04	5.37E–05
	0.947	0.248	0.461	1.433	18 months	'If always treated' versus 'If never treated'	1.35E–04	4.05E–03	2.89E–04
TC	0.15	0.059	0.035	0.266	6 months	'If always treated' versus 'If never treated'	1.09E–02	3.27E–01	1.26E–02
	0.203	0.077	0.053	0.352	9 months	'If always treated' versus 'If never treated'	8.12E–03	2.44E–01	9.74E–03
	0.248	0.064	0.124	0.373	12 months	'If always treated' versus 'If never treated'	9.42E–05	2.83E–03	2.36E–04
	0.289	0.075	0.142	0.437	15 months	'If always treated' versus 'If never treated'	1.22E–04	3.66E–03	2.82E–04
	0.283	0.084	0.118	0.447	18 months	'If always treated' versus 'If never treated'	7.38E–04	2.21E–02	1.11E–03
HDL	−0.074	0.007	−0.088	−0.06	6 months	'If always treated' versus 'If never treated'	5.75E–25	1.73E–23	1.73E–23
	−0.062	0.013	−0.088	−0.036	9 months	'If always treated' versus 'If never treated'	2.28E–06	6.84E–05	1.14E–05
	−0.069	0.012	−0.093	−0.046	12 months	'If always treated' versus 'If never treated'	4.58E–09	1.37E–07	4.58E–08
	−0.069	0.015	−0.099	−0.039	15 months	'If always treated' versus 'If never treated'	5.47E–06	1.64E–04	1.82E–05
	−0.064	0.018	−0.099	−0.029	18 months	'If always treated' versus 'If never treated'	3.63E–04	1.09E–02	6.05E–04
LDL	0.098	0.041	0.017	0.178	6 months	'If always treated' versus 'If never treated'	1.82E–02	5.46E–01	1.92E–02
	0.145	0.062	0.024	0.266	9 months	'If always treated' versus 'If never treated'	1.86E–02	5.58E–01	1.92E–02
	0.189	0.048	0.095	0.283	12 months	'If always treated' versus 'If never treated'	7.65E–05	2.30E–03	2.09E–04
	0.215	0.058	0.101	0.329	15 months	'If always treated' versus 'If never treated'	2.19E–04	6.57E–03	4.09E–04
	0.205	0.062	0.083	0.327	18 months	'If always treated' versus 'If never treated'	9.58E–04	2.87E–02	1.37E–03
Triglycerides	0.212	0.076	0.063	0.36	6 months	'If always treated' versus 'If never treated'	5.36E–03	1.61E–01	6.70E–03
	0.241	0.065	0.113	0.368	9 months	'If always treated' versus 'If never treated'	2.27E–04	6.81E–03	4.09E–04
	0.028	0.261	−0.484	0.54	12 months	'If always treated' versus 'If never treated'	9.15E–01	1.00E+00	9.15E–01
	0.346	0.054	0.24	0.452	15 months	'If always treated' versus 'If never treated'	1.49E–10	4.47E–09	2.24E–09
	0.36	0.062	0.238	0.481	18 months	'If always treated' versus 'If never treated'	6.82E–09	2.05E–07	5.12E–08

1) The interval between each time point was 3 months.
2) Definition of treatment: treatment with clozapine or olanzapine. The time-varying confounders included the treatment status of four other drugs, including metformin, atorvastatin, simvastatin, and valproate. Please refer to the main text for details.
3) ATE indicates the difference in the average treatment effect between patients taking clozapine or olanzapine and those taking other SGAs.
4) Abbreviations: TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; FG, fasting blood glucose level; BMI, body mass index.

though its exclusion showed slightly larger treatment effects, suggesting aripiprazole has minimal metabolic impact (Table 1 and Supplementary Table S6).

Fourth, using an interval-based treatment definition (>80% SGA use) showed similar patterns but smaller treatment effects, compared to point-based definition. For example, the 12-month ATE of SGAs on BMI was 0.811 kg/m² (95% CI = 0.63−0.991) for point-based versus 0.379 kg/m² (95% CI = 0.196−0.562) for interval-based analysis (Table 1 and Supplementary Table S5). Though smaller, these effects remained significant, supporting robustness of our findings.

To address irregular outcome measurements, we employed both single and multiple imputation methods with linear mixed models to generate regular interval data. Results from both approaches demonstrated comparable estimates (Supplementary Table S8), supporting the robustness of our findings. Additionally, we dichotomized the continuous metabolic parameters to evaluate the odds ratio (OR) of abnormal outcomes between the 'if always treated' versus 'if never treated' (Supplementary Table S9) and different duration of treatment vs 'if never treated' scenarios (Supplementary Table S10). The conclusions remain largely similar (see supplementary text).

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Table 3. Average treatment effect (ATE) of SGAs comparing different time of SGA discontinuation with the never treated

Outcome	ATE	Std.error	CI_0.025	CI_0.975	Treatment	Never	Follow_up_length	P_value	P_adjust_bonferroni	P_adjust_fdr
FG	0.002	0.048	−0.091	0.096	abar_1_0_0_0	abar_0_0_0_0	12	9.59E−01	1.00E+00	9.59E−01
	0.047	0.048	−0.047	0.142	abar_1_1_0_0	abar_0_0_0_0	12	3.28E−01	1.00E+00	7.16E−01
	−0.033	0.049	−0.129	0.063	abar_1_1_1_0	abar_0_0_0_0	12	5.00E−01	1.00E+00	8.57E−01
	0.09	0.04	0.012	0.169	abar_1_1_1_1	abar_0_0_0_0	12	2.35E−02	5.64E−01	6.27E−02
BMI	0.326	0.143	0.045	0.607	abar_1_0_0_0	abar_0_0_0_0	12	2.29E−02	5.50E−01	6.27E−02
	0.556	0.139	0.284	0.828	abar_1_1_0_0	abar_0_0_0_0	12	6.20E−05	1.49E−03	3.72E−04
	0.35	0.146	0.064	0.635	abar_1_1_1_0	abar_0_0_0_0	12	1.65E−02	3.96E−01	5.66E−02
	0.811	0.092	0.63	0.991	abar_1_1_1_1	abar_0_0_0_0	12	1.41E−18	3.38E−17	3.38E−17
TC	−0.029	0.058	−0.142	0.083	abar_1_0_0_0	abar_0_0_0_0	12	6.09E−01	1.00E+00	8.98E−01
	0.019	0.057	−0.094	0.132	abar_1_1_0_0	abar_0_0_0_0	12	7.39E−01	1.00E+00	9.33E−01
	−0.032	0.06	−0.149	0.084	abar_1_1_1_0	abar_0_0_0_0	12	5.87E−01	1.00E+00	8.98E−01
	0.146	0.05	0.048	0.244	abar_1_1_1_1	abar_0_0_0_0	12	3.61E−03	8.66E−02	1.44E−02
HDL	0.007	0.008	−0.008	0.022	abar_1_0_0_0	abar_0_0_0_0	12	3.66E−01	1.00E+00	7.32E−01
	−0.004	0.008	−0.02	0.012	abar_1_1_0_0	abar_0_0_0_0	12	6.36E−01	1.00E+00	8.98E−01
	0.001	0.008	−0.016	0.017	abar_1_1_1_0	abar_0_0_0_0	12	9.44E−01	1.00E+00	9.59E−01
	−0.032	0.006	−0.044	−0.02	abar_1_1_1_1	abar_0_0_0_0	12	2.33E−07	5.59E−06	1.86E−06
LDL	0.009	0.046	−0.082	0.1	abar_1_0_0_0	abar_0_0_0_0	12	8.43E−01	1.00E+00	9.59E−01
	0.032	0.046	−0.058	0.122	abar_1_1_0_0	abar_0_0_0_0	12	4.85E−01	1.00E+00	8.57E−01
	−0.009	0.046	−0.098	0.08	abar_1_1_1_0	abar_0_0_0_0	12	8.46E−01	1.00E+00	9.59E−01
	0.121	0.04	0.042	0.2	abar_1_1_1_1	abar_0_0_0_0	12	2.62E−03	6.29E−02	1.26E−02
Triglycerides	0.004	0.044	−0.083	0.091	abar_1_0_0_0	abar_0_0_0_0	12	9.27E−01	1.00E+00	9.59E−01
	0.069	0.056	−0.041	0.18	abar_1_1_0_0	abar_0_0_0_0	12	2.21E−01	1.00E+00	5.30E−01
	0.023	0.054	−0.084	0.129	abar_1_1_1_0	abar_0_0_0_0	12	6.78E−01	1.00E+00	9.04E−01
	0.241	0.044	0.155	0.328	abar_1_1_1_1	abar_0_0_0_0	12	4.82E−08	1.16E−06	5.78E−07

1) The interval between each time-point was 3 months.
2) The definition of treatment (7 SGAs): taking any of these SGAs, including clozapine, olanzapine, amisulpride, paliperidone, risperidone, quetiapine, or lurasidone; the definition of time-varying confounders (4 drugs): taking any of these drugs, including metformin, atorvastatin, simvastatin, or valproate.
3) Treatment is coded as 1 if the patient took SGAs at the observed time point and 0 otherwise. For example, abar_1_0_0_0 indicates SGA treatment at the 1st time-point (3rd month) but not afterwards.
4) Abbreviation: TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; FG, fasting blood glucose level; BMI, body mass index.

Discussion

In this study, we applied a longitudinal TMLE framework to study the joint effect of SGAs on metabolic indicators, including TC, HDL, LDL, BMI, triglycerides, and FG. We estimated the ATE of being treated with SGAs for 6, 9, 12, 15, and 18 months. In addition, we studied the impact of treatment discontinuation on different outcomes. Sensitivity analyses were performed to validate the results.

Main findings

In general, the ATEs for BMI and TG showed an increasing trend from 6 to 12 months, followed by a decline from 12 to 18 months. A similar pattern was observed for TC and LDL, with peak ATEs at 15 months. This suggests that while metabolic side effects increase early in treatment, they stabilize over time, consistent with previous findings that antipsychotic-induced lipid changes tend to stabilize [9] after an initial worsening.

Notably, ATEs peaked around 12–15 months before slightly decreasing. This may reflect patients' efforts to counteract side effects, such as diet changes and increased physical activity, which were not captured in our dataset. Alternatively, patients may have developed 'resilience' to side effects over time, though this warrants further study. For HDL and FG, we observed different patterns. For HDL, fluctuations were observed, with a clearer pattern of decrease followed by an increase in ATE emerging at 1-month intervals. This may be due to more frequent observations providing additional information over the same follow-up. FG showed significantly positive ATEs across follow-up, indicating SGAs' adverse impact, though the increase plateaued earlier than other outcomes. Additionally, a lingering effect of SGAs on BMI was observed (Table 3 and Supplementary Figure S2). BMI remained elevated across different treatment sequences compared with no treatment, even after discontinuation of SGAs before the end of follow-up (Table 3).

Relatively few studies have examined the long-term (>1 year) effects of SGAs on a comprehensive panel of metabolic parameters in schizophrenia. Vázquez-Bourgon et al. found that discontinuing

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antipsychotics after 10 years improved metabolic profiles, including less weight gain, but patients still had worse profiles than healthy controls, suggesting metabolic side effects may persist (Vázquez-Bourgon et al., 2021). In this study, we primarily found BMI to be persistently affected, contrary to Vázquez-Bourgon et al.'s findings that other metabolic parameters (e.g. HDL, TG, and insulin resistance) were persistently affected. However, Vázquez-Bourgon et al. compared treatment discontinuers with healthy controls instead of other psychosis subjects, making it difficult to isolate the specific effects of SGAs from the metabolic impacts of psychosis itself. In another study, Mackin et al. (Mackin, Waton, Watkinson, & Gallagher, 2012) compared patients who discontinued SGAs to those receiving continuous treatments and reported that BMI and waist circumference increased in both groups, with no significant difference over 4 years. Besides, they did not find any significant difference in glucose and lipid measures. However, Mackin et al.'s study (Mackin, Waton, Watkinson, & Gallagher, 2012) had a small sample size (89 subjects only). Taken together, the current and prior studies provided evidence that the metabolic effects of SGAs may persist to varying degrees, even after medication discontinuation, though more research with larger samples is needed. The persistence of weight gain after discontinuation of SGAs seemed to be a consistent finding, although other metabolic outcomes showed mixed results across studies. Finally, consistent with earlier findings (Huhn et al., 2019), we also observed larger ATEs when comparing clozapine/olanzapine with other SGAs (Table 2).

Clinical implications

Our findings have several clinical implications. The observation that BMI remains elevated after SGA discontinuation is a potentially important finding for clinicians and patients. Our findings suggest that certain metabolic side effects of SGAs may be relatively long-lasting, even after treatment cessation. Ongoing monitoring of weight/BMI or other obesity indicators, and measures to promote a healthy weight, such as proper diet and exercise, may be beneficial even after SGA discontinuation.

On the other hand, we did not observe any lingering side effects on other metabolic measures, provided that SGAs have been discontinued for at least 3 months. This suggests that lingering adverse metabolic effects, if present, may be less pronounced for other metabolic measures. However, it should be noted that non-significant results may be due to insufficient power to detect modest differences.

In addition, we observed that with continuation of SGAs, metabolic side effects increased quickly and peaked at around 12–15 months. These findings may be useful for counseling patients on the naturalistic progression of metabolic side effects. Clinicians and patients should be particularly aware of the metabolic side effects emerging in the first 12–15 months of SGA prescription, with possibly more frequent monitoring during this period.

Nevertheless, regardless of the treatment duration, the metabolic outcomes for those on continuous SGA therapy were consistently worse compared to those never on SGAs. This underscores the importance of careful consideration of SGA prescription, and continuous monitoring and management of metabolic health for all patients on these drugs.

Moreover, clozapine and olanzapine were found to be more strongly linked to greater metabolic side effects than other SGAs. While stronger metabolic side effects of these drugs have been reported, we provide further support for these findings using a rigorous *causal* statistical framework which accounts for *time-varying* confounding and treatment status.

Strengths and limitations

Our study has several notable strengths, including the use of a longitudinal TMLE framework to assess SGA side effects on six metabolic parameters, while controlling for confounders. Second, we evaluated dynamic *sequences* of treatments, allowing for SGA treatment status changes during follow-up, and addressed varying follow-up durations across time-points. These are challenging to evaluate in RCTs.

Third, LTMLE is a doubly robust model, yielding consistent estimates as long as either the outcome model or the treatment mechanism is correctly specified, even if the other model is misspecified. It differs from traditional methods that usually depend on a single model.

Fourth, prescription changes were meticulously recorded and integrated into the LTMLE model, a level of detail often missing in prior studies (Rummel-Kluge et al., 2010). Sensitivity analyses, including varying time intervals and treatment definitions, confirmed the robustness of our findings. Additionally, our study examined a wide range of metabolic outcomes, offering an in-depth understanding of SGA long-term side effects.

Methodologically, this study demonstrates how LTMLE can provide clinical insights into SGA's metabolic side effects while addressing the *dynamic* nature of treatment sequences. To our knowledge, very few psychopharmacology studies have considered treatment sequences, making our work a valuable template for future research in this underexplored area (Rummel-Kluge et al., 2010).

Our study also has several limitations. Due to the small sample size, we only compared clozapine/olanzapine with other SGAs, without analyzing each SGA's specific longitudinal effects. Non-significant results may also reflect insufficient power to detect small effects. Additionally, as an observational study, unobserved confounders may exist, although we used advanced statistical methods to account for complex, time-varying confounders. Particularly, lifestyle factors, such as diet, physical activity, and smoking behaviors, were not captured, which could influence the metabolic outcomes. Also, illness duration was not modelled, as the duration of untreated psychosis was not evaluated in our study. Finally, we did not evaluate the effects of different medication dosages as the LTMLE approach is designed for binary treatments only. Additionally, standardizing dosages across different medications is complex.

In conclusion, the ATEs of SGAs on metabolic parameters (BMI, TG, TC, and LDL) increased up to 12–15 months before declining, suggesting metabolic side effects tend to stabilize over time. While BMI may show lingering effects after SGA discontinuation, other metabolic parameters did not. Larger studies are needed to confirm these findings.

Supplementary material. The supplementary material for this article can be found at http://doi.org/10.1017/S0033291725000935.

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Ethical statements. Ethical approval was obtained from the New Territories West Cluster Ethics Committee (approval numbers: NTWC/CREC/823/10 and NTWC/CREC/1293/14) and the Joint Chinese University of Hong Kong-New Territories East Cluster Clinical Research Ethics Committee (approval number: 2016.559). All participants provided written informed consent.

Competing interests. All authors declare that they have no conflict of interest.

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