Original Investigation | META-ANALYSIS

Type 2 Diabetes Mellitus in Youth Exposed to Antipsychotics
A Systematic Review and Meta-analysis

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IMPORTANCE Antipsychotics are used increasingly in youth for nonpsychotic and off-label indications, but cardiometabolic adverse effects and (especially) type 2 diabetes mellitus (T2DM) risk have raised additional concern.

OBJECTIVE To assess T2DM risk associated with antipsychotic treatment in youth.

DATA SOURCES Systematic literature search of PubMed and PsycINFO without language restrictions from database inception until May 4, 2015. Data analyses were performed in July 2015, and additional analyses were added in November 2015.

STUDY SELECTION Longitudinal studies reporting on T2DM incidence in youth 2 to 24 years old exposed to antipsychotics for at least 3 months.

DATA EXTRACTION AND SYNTHESIS Two independent investigators extracted study-level data for a random-effects meta-analysis and meta-regression of T2DM risk.

MAIN OUTCOMES AND MEASURES The coprimary outcomes were study-defined T2DM, expressed as cumulative T2DM risk or as T2DM incidence rate per patient-years. Secondary outcomes included the comparison of the coprimary outcomes in antipsychotic-treated youth with psychiatric controls not receiving antipsychotics or with healthy controls

RESULTS Thirteen studies were included in the meta-analysis, including 185 105 youth exposed to antipsychotics and 310 438 patient-years. The mean (SD) age of patients was 14.1 (2.1) years, and 59.5% were male. The mean (SD) follow-up was 1.7 (2.3) years. Among them, 7 studies included psychiatric controls (1 342 121 patients and 2 071 135 patient-years), and 8 studies included healthy controls (298 803 patients and 463 084 patient-years). Antipsychotic-exposed youth had a cumulative T2DM risk of 5.72 (95% CI, 3.45-9.48; $P < .001$) per 1000 patients. The incidence rate was 3.09 (95% CI, 2.35-3.82; $P < .001$) cases per 1000 patient-years. Compared with healthy controls, cumulative T2DM risk (odds ratio [OR], 2.58; 95% CI, 1.56-4.24; $P < .0001$) and incidence rate ratio (IRR) (IRR, 3.02; 95% CI, 1.71-5.35; $P < .0001$) were significantly greater in antipsychotic-exposed youth. Similarly, compared with psychiatric controls, antipsychotic-exposed youth had significantly higher cumulative T2DM risk (OR, 2.09; 95% CI, 1.50-52.90; $P < .0001$) and IRR (IRR, 1.79; 95% CI, 1.31-2.44; $P < .0001$). In multivariable meta-regression analyses of 10 studies, greater cumulative T2DM risk was associated with longer follow-up ($P < .001$), olanzapine prescription ($P < .001$), and male sex ($P = .002$) ($r^2 = 1.00$, $P < .001$). Greater T2DM incidence was associated with second-generation antipsychotic prescription ($P \leq .050$) and less autism spectrum disorder diagnosis ($P = .048$) ($r^2 = 0.21$, $P = .044$).

CONCLUSIONS AND RELEVANCE Although T2DM seems rare in antipsychotic-exposed youth, cumulative risk and exposure-adjusted incidences and IRRs were significantly higher than in healthy controls and psychiatric controls. Olanzapine treatment and antipsychotic exposure time were the main modifiable risk factors for T2DM development in antipsychotic-exposed youth. Antipsychotics should be used judiciously and for the shortest necessary duration, and their efficacy and safety should be monitored proactively.

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Antipsychotics are used increasingly in youth for many psychiatric disorders, particularly second-generation antipsychotics (SGAs).[1-3] Although antipsychotic use in youth had long been restricted to schizophrenia spectrum disorders,[4,5] significant data for SGA efficacy have accumulated for nonpsychotic disorders, leading to regulatory approval for bipolar mania and irritability associated with autistic disorder and Tourette syndrome.[6-9] However, antipsychotic use in youth has broadened substantially to many off-label indications,[10,11] including impulsivity, mood dysregulation, aggressive behaviors, depression, and anxiety.[12-15]

Antipsychotic efficacy should be balanced against adverse effects, which requires adequate information concerning their short-term and (especially) long-term risks. Yet, little is known about long-term risks.[16,17] Compared with first-generation antipsychotics (FGAs), SGAs have significantly fewer neuromotor adverse effects but generally have more cardiometabolic consequences, including weight gain, dyslipidemia, and type 2 diabetes mellitus (T2DM).[16,18-20] Because cardiometabolic effects, which can start even after short antipsychotic exposure and at low dosages,[18,19,21] are associated with increased morbidity and premature mortality, they are a current focus of concern.[18,22]

Cardiometabolic adverse effects of antipsychotics tend to appear faster and to a greater extent in youth than in adults.[21,23,24] Antipsychotic treatment results in relevant weight gain in a significant proportion of youth.[23,25-27] Whether this overall heightened risk of short-term cardiometabolic adverse effects in youth compared with adults is due to developmental differences or because of less prior antipsychotic exposure and lifetime antipsychotic-related weight gain remains debated.[16,17,21]

In adults, there is a clear link between antipsychotic treatment and impaired glucose tolerance, insulin resistance, and risk for T2DM that seems to differ across agents,[28-30] with the most serious concerns revolving around SGAs.[31-33] Despite the substantial use of SGAs in youth, far less is known about the T2DM risk in children and adolescents than in adults treated with antipsychotics.[34-36]

Given these uncertainties, a much smaller available database regarding the difficult-to-study long-term antipsychotic adverse effects in young people, and the importance of T2DM as a potential risk factor for cardiovascular disease,[37] we conducted a systematic review and meta-analysis to assess the incidence of T2DM in antipsychotic-exposed youth compared with psychiatric controls and healthy controls. In addition, we sought to identify potential moderators of T2DM risk. Based on the literature in adults, we hypothesized that antipsychotic treatment would be associated with significantly greater T2DM risk than in both control groups.

Methods

This systematic review was conducted in accord with the Meta-analysis of Observational Studies in Epidemiology[38] guidelines and the Preferred Reporting Items for Systematic Reviews and Meta-analyses[39] standard.

Literature Search

Two independent authors (B.G. and A.R.) searched PubMed/MEDLINE and PsycINFO without language restrictions from database inception until May 4, 2015, using the following search terms: (*child** OR *adolescent** OR *pediatric* OR *youth*) and (*antipsych** OR *neuroleptic*) and (*hemoglobin A1C* OR *HbA1C* OR *glucose* OR *hyperglycemia* OR *diabetes* OR *prediabetes* OR *insulin* OR *hyperinsulinemia*). The electronic search was supplemented by a manual review of reference lists from eligible publications and relevant reviews. Authors were contacted for additional information.

Inclusion Criteria

We included longitudinal studies reporting on the incidence of T2DM (defined by American Diabetes Association[40] criteria), prescription of antidiabetic medications, or recorded medical diagnosis of T2DM in at least 20 youth 0 to 24 years old exposed to antipsychotics for at least 3 months. When available, T2DM incidence data were included from psychiatric controls unexposed to antipsychotics or from healthy controls. Studies of individuals with T2DM at baseline that reported on the proportion receiving antipsychotics were ineligible for inclusion.

Data Abstraction

Two of us (B.G. and A.R.) abstracted all data, and any inconsistencies were resolved by consensus or by a third author (C.U.C.). When articles reported on overlapping samples, details of the largest study sample for each respective outcome were included.

Data Analysis

Demographic information about the pooled study samples was calculated by weighting the study mean values according to sample size. The unadjusted, cumulative T2DM risk was computed as the number of patients with new onset of study-defined T2DM divided by the number of individuals free of T2DM diagnosis and T2DM treatment at baseline. Incidence rates per patient-year were computed by dividing the number of patients with study-defined T2DM by the number of patient-years of follow-up. Odds ratios (ORs) and 95% CIs were computed by comparing the unadjusted, cumulative T2DM risk in youth exposed to antipsychotics vs the unadjusted, cumulative T2DM risk in psychiatric control youth or healthy control youth and between the 2 control groups. Incidence rate ratios (IRRs) and 95% CIs were used to compare the T2DM incidence rates per patient-year in antipsychotic-exposed youth vs psychiatric control youth or healthy control youth and between the 2 control groups. Data were analyzed with a software program (Comprehensive Meta-Analysis, version 2; http://www.meta-analysis.com). All analyses used a random-effects model[41] and were 2-sided, with $\alpha = .05$. Heterogeneity was assessed with the I^2 statistic,[42] where I^2 of at least 50% indicated significant heterogeneity. The number needed to harm (NNH) was calculated by dividing 1 by the risk difference.

We also conducted exploratory subgroup, sensitivity, and meta-regression analyses to identify potential moderators of

the unadjusted, cumulative T2DM risk and incidence rate in antipsychotic-exposed youth. The subgroup analyses examined whether the T2DM risk was replicated when separately analyzing studies restricting their sample to youth 18 years and younger. The sensitivity analyses examined whether the T2DM risk was replicated when separately analyzing (1) studies with different T2DM definitions, (2) studies that potentially included type 1 diabetes mellitus (T1DM), (3) studies that potentially included patients with a prescription of oral antidiabetic medications for reasons other than T2DM, and (4) studies after excluding one study[23] with 100% olanzapine-treated youth.

After excluding a significant effect of study quality using the Newcastle-Ottawa Scale[43] (NOS) on the results, a backward elimination mixed random-effects meta-regression analysis was conducted with the initial variables of sex, age, sample size, percentage of patients with specific psychiatric diagnoses, and percentage of patients receiving SGAs (pooled). A second meta-regression analysis replaced pooled SGAs with percentage of patients receiving specific SGAs. Variables were entered into the initial backward elimination model if in univariable analyses they reached $P < .20$. Publication bias was assessed with the funnel plot, Egger regression test,[44] and the "trim and fill" method.[45] Finally, descriptive statistical methods were used for the exploratory summary of study-reported correlates of T2DM incidence based on patient-level data not available for study-level meta-regression analyses.

Results

The initial search produced 4647 results, and 4517 studies were excluded on the title or abstract level. Of the remaining 130 references, 117 were excluded after full-text review, yielding 13 meta-analyzable studies[23,34,35,46-55] (1 study reported on 2 subsets based on antipsychotic class) (eFigure in the Supplement).

Study Characteristics

Eleven studies[34,35,47,48,50-55] (n = 1 825 343) were retrospective database investigations, 2 studies[46,49] (n = 565) were prospective naturalistic cohort investigations, and 1 study[23] (n = 121) pooled data from 6 prospective olanzapine investigations. The mean (SD) NOS score was 7.4 (1.8), and the median NOS score was 8. Twelve of the 13 studies of antipsychotic-exposed youth provided information on the mean (SD) follow-up duration, which was 1.7 (2.3) years (310 438 patient-years). The study quality was high overall, with scores between 7 and 9 on the NOS in all but 2 studies, which had scores of 3 and 4, respectively (eTable 1 in the Supplement).

Eight studies[34,46-48,50,52,55] compared data with a healthy control group, and the mean (SD) follow-up was 1.6 (2.9) years (463 084 patient-years). Seven studies[34,35,47,48,51,53,54] had a psychiatric control group, with a mean (SD) follow-up of 1.6 (3.1) years (2 071 135 patient-years). Two studies[23,49] did not have a control group (**Table 1**).

Patient and Treatment Characteristics

The mean (SD) age of the antipsychotic-exposed sample (n = 185 105) was 14.1 (2.1) years (age range, 2-24 years), and a mean (SD) of 59.5% (8.0%) were male. The mean (SD) age of the psychiatric controls (n = 1 342 121) was 13.8 (1.1) years (age range, 5-24 years), and a mean (SD) of 55.7% (9.2%) were male. The mean (SD) age of the healthy controls (n = 298 803) was 13.9 (3.2) years (age range, 4-19 years), and a mean (SD) of 52.6% (9.0%) were male.

In the antipsychotic-exposed sample, most had a disruptive behavior disorder (DBD) or attention-deficit/hyperactivity disorder (ADHD) (in 46.9%) or a mood spectrum disorder, including mood disorder not otherwise specified (in 22.8%,), depression (in 26.9%), bipolar disorder (BPD) (in 16.2%), and BPD or psychosis (in 5.1%). Less commonly observed were anxiety disorders (in 7.9%), psychosis (in 5.7%), pervasive developmental disorder or autism (in 5.3%), substance abuse disorder (in 4.6%), and tic disorders (in 0.0003%). In the psychiatric control group, the psychiatric diagnoses were mainly DBD or ADHD (in 51.8%) and mood spectrum disorder (in 34.1%). Other diagnoses included anxiety disorders (in 8.7%), pervasive developmental disorder or autism (in 5.4%), psychosis (in 0.3%), and substance use disorders (in 0.2%).

All but one study[53] provided general information regarding antipsychotic treatment class, consisting predominantly of SGAs (in 94.9% [n = 169 621]), with few youth being treated with FGAs (in 3.7% [n = 6744]) or combinations of 2 or more antipsychotics (in 2.4% [n = 4309]). In 10 studies with specific antipsychotic use data, risperidone was the most commonly used (41.7%), followed by quetiapine fumarate (26.6%), aripiprazole (17.2%), and olanzapine (10.2%).

Outcome Definitions

The analyzed studies used the following definitions of T2DM: (1) the prescription of an antidiabetic medication or a clinical diagnosis of T2DM (6 studies[35,47,50,53-55] [42.9%]), (2) T2DM diagnosis based on a fasting blood glucose level of at least 126 mg/dL (2 studies[23,46] [14.3%]) (to convert glucose level to millimoles per liter, multiply by 0.0555), (3) a recorded T2DM diagnosis and antidiabetic medication prescription (2 studies[52] [14.3%]), (4) an antidiabetic medication prescription only (1 study[51] with 2 separate samples [7.2%]), (5) a clinical diagnosis of T2DM only (1 study[48] [7.2%]), (6) a questionnaire-based T2DM diagnosis (1 study[49] [7.2%]), or (7) a T2DM diagnosis, antidiabetic medication, glycated hemoglobin level of at least 7%, or random plasma glucose level of at least 200 mg/dL (1 study[34] [7.2%]). Regarding T2DM definition, 7 studies[23,34,46,47,49,50,53] potentially included cases of T1DM, while 5 studies[34,47,50,53,54] would have potentially included patients treated with oral antidiabetic medications for reasons other than T2DM (Table 1). Procedures to reduce confounding, including matching and multivariable analysis, are summarized in eTable 2 in the Supplement.

T2DM in Antipsychotic-Exposed Youth, Psychiatric Controls, and Healthy Controls

The meta-analytically calculated T2DM risk was highest in the antipsychotic-exposed cohort, with an unadjusted, cumulative risk of 5.72 (95% CI, 3.45-9.48) per 1000 patients and an incidence rate of 3.09 (95% CI, 2.35-3.82) per 1000 patient-years ($P < .001$ for both). The risk was intermediate in psychiatric

Table 1. Study, Sample, and Treatment Characteristics, With Total Mean Values Weighted by Sample Size

	Study						Antipsychotic-Exposed Youth						
Source	Design	NOS Score	T2DM Definition	T1DM Inclusion	Oral Antidiabetic Medication for Other Indication	Follow-up, y	No.	Age, Mean (Range), y	Male Sex, %	Most Common Diagnoses, %	Most Common Antipsychotics, %	Healthy Controls, No.	Psychiatric Controls, No.
Andrade et al,[34] 2011	RDS	7	Diagnosis of T2DM, prescription of antidiabetic medication, glycated hemoglobin level ≥7%, or random plasma glucose level ≥200 mg/dL	Potentially	Potentially	0.38	9636	NA (5-18)	60	55.2 DBD and 68.5 MD	100 SGA	38 544	26 265 (Antidepressant)
Arango et al,[46] 2014	PCS	6	T2DM diagnosis based on fasting blood glucose level ≥126 mg/dL	Potentially	No	0.49	248	14.6 (4-17)	62	33.9 Psychosis, 29.0 MD, 18.9 DBD	63.3 Risperidone, 17.7 olanzapine, 19.0 quetiapine	15	Not applicable
Bobo et al,[35] 2013	RDS	8	Prescription of antidiabetic medication (except exclusive insulin treatment)or a diagnosis of T2DM	No	No[a]	1.32	28 858	14.5 (6-24)	56	70.9 MD, 38.9 ADHD, 25.3 CD, 20.6 anxiety, 12.0 SA	37 Risperidone, 20 quetiapine, 20 olanzapine	Not applicable	14 429
Enger et al,[47] 2013	RDS	8	Prescription of antidiabetic medication or a diagnosis of T2DM	Potentially	Potentially	1.31	9350	15.2 (13-17)	50.5	100 Schizophrenia or BPD	94.9SGA	188 784	8740 (Schizophrenia or BPD)
Guo et al,[53] 2006	RDS	8	Prescription of antidiabetic medication or a diagnosis of T2DM	Potentially	Potentially	NR	3052	13.22 (≤17)	57.7	100 BPD	NR	Not applicable	14 469 (BPD)
Harrison-Woolrych et al,[49] 2007	PCS	3	Questionnaire-based T2DM diagnosis	Potentially	No	2.37	420	10.0 (2-15)	78	43 DBD or ADHD, 34 PDD, 17 developmental disorder	93 Risperidone	Not applicable	Not applicable
Kryzhanovskaya et al,[23] 2012	POS	4	T2DM diagnosis based on fasting blood glucose level ≥126 mg/dL	Potentially	No	0.55	179	15.8 (13-18)[b]	69	47.5 Psychosis, 45.2 BPD[b]	100 Olanzapine	Not applicable	Not applicable
Liao et al,[52] 2011	RDS	9	Recorded T2DM diagnosis and prescription of antidiabetic medication	No	No	1.42	1999	15.8 (10-19)	52.9	100 Schizophrenia	100 FGA	19 990	Not applicable
						1.77	989	16.1 (10-19)	47.9	100 Schizophrenia	100 SGA	9890	Not applicable
McIntyre and Jerrell,[48] 2008	RDS	8	Clinical diagnosis of T2DM	No	No	8.81	4140	Mean (SD), 10.4 (3.6)	68.2	8.6 Schizophrenia, 54.6 major affective disorder, 27.8 other psychotic disorder, 71.7 CD or ODD, 78.7 ADHD	39.5 Risperidone, 42.4 combination of ≥2 antipsychotics	4500	15 738 (Antimanic or antidepressant medication)

(continued)

Table 1. Study, Sample, and Treatment Characteristics, With Total Mean Values Weighted by Sample Size (continued)

	Study						Antipsychotic-Exposed Youth						
Source	Design	NOS Score	T2DM Definition	T1DM Inclusion	Oral Antidiabetic Medication for Other Indication	Follow-up, y	No.	Age, Mean (Range), y	Male Sex, %	Most Common Diagnoses, %	Most Common Antipsychotics, %	Healthy Controls, No.	Psychiatric Controls, No.
Morrato et al,[50] 2010	RDS	8	Prescription of antidiabetic medication or a diagnosis of T2DM	Potentially	Potentially	0.49	5370	NA (6-17)	63.9	48.1 Severe mental illness (schizophrenia or schizoaffective disorder/psychosis)	100 SGA, 50.5 risperidone	15 000 (albuterol)	Not applicable
Nielsen et al,[51] 2014	RDS	8	Prescription of antidiabetic medication (except exclusive insulin treatment)	No	No	4.5	7253	14.4	58.3	23.9 Psychosis; 21.9 neurotic, somatoform, or stress-related disorder; 15.7 MD; 12.7 PDD or autism; 12.6 DBD or ADHD	19.1 Aripiprazole, 19.2 quetiapine, 24.7 risperidone, 14.1 chlorprothixene	Not applicable	41 046
Rubin et al,[54] 2015	RDS	8	Prescription of antidiabetic medication (except exclusive insulin treatment) or a diagnosis of T2DM	No	Potentially	1.59	107 551	14.1 (10-18)	60.9	53.5 ADHD; 45.6 CD; 40.2 depression; 19.5 BPD; 14.8 developmental delay; 11.5 anxiety; 10.5 intellectual disability	38.9 Risperidone, 27.0 quetiapine, 19.9 aripiprazole	Not applicable	1 221 434
Sohn et al,[55] 2015	RDS	9	Prescription of antidiabetic medication (except exclusive insulin treatment) or a diagnosis of T2DM	No	No	1.3	6236	12 (4-18)	61	22.7 ADHD; 17.9 psychosis; 16 depression; 10.4 BPD	40.1 Risperidone, 31.4 aripiprazole, 22.1 quetiapine	22 080	Not applicable
Total	13 Studies (14 cohorts)	Mean (SD), 7.4 (1.8)	NA	NA	NA	1.7	185 105	14.1 (2-24)	59.5	46.9 DBD or ADHD; 26.8 depression; 22.8 MD; 16.2 BPD	94.9 SGA (41.7 risperidone, 26.6 quetiapine, 17.2 aripiprazole, 10.2 olanzapine)	8 Studies (n = 298 803)	7 Studies (n = 1 342 121)

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; BPD, bipolar disorder; CD, conduct disorder; DBD, disruptive behavior disorder; FGA, first-generation antipsychotic; MD, mood disorder; NA, not available; NOS, Newcastle-Ottawa Scale; NR, not reported; ODD, oppositional defiant disorder; PCS, prospective cohort study; PDD, pervasive developmental disorder; POS, prospective open-label study; RDS, retrospective database study; SA, substance abuse; SGA, second-generation antipsychotic; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

SI conversion factors: To convert glucose level to millimoles per liter, multiply by 0.0555; to convert glycated hemoglobin level to proportion of total hemoglobin, multiply by 0.01.

[a] Medication at least 6 months before diabetes, end of study, loss to follow-up, or death (n = 3800).

[b] Of the complete sample (n = 179).

Table 2. Unadjusted, Cumulative T2DM Risk and Incidence Rates in Antipsychotic-Exposed Youth, Healthy Controls, and Psychiatric Controls

	Antipsychotic-Exposed Youth[a]			Healthy Controls[b]			Psychiatric Controls[c]		
Variable	Event Rate (95% CI) per 1000 Patients	*P* Value[d]	I^2 Statistic, %	Event Rate (95% CI) per 1000 Patients	*P* Value[d]	I^2 Statistic, %	Event Rate (95% CI) per 1000 Patients	*P* Value[d]	I^2 Statistic, %
Unadjusted, cumulative T2DM risk per 1000 patients	5.72 (3.45-9.48)	<.001	99.5	2.15 (0.84-5.47)	<.001	98.8	2.61 (0.80-8.52)	<.001	99.8
Group Comparison	**Odds Ratio (95% CI)**			**Odds Ratio (95% CI)**			**Odds Ratio (95% CI)**		
Healthy controls	2.58 (1.56-4.24)	<.001	86.2	NA	NA	NA	NA	NA	NA
Psychiatric controls	2.09 (1.50-2.90)	<.001	87.2	1.57 (1.29-1.90)	<.001	0.0	NA	NA	NA
Variable	**Incidence Rate (95% CI) per 1000 Patient-Years**			**Incidence Rate (95% CI) per 1000 Patient-Years**			**Incidence Rate (95% CI) per 1000 Patient-Years**		
T2DM incidence rate per 1000 patient-years	3.09 (2.35-3.82)	<.001	78.3	1.28 (0.78-1.79)	<.001	95.8	1.74 (1.10-2.38)	<.001	98.1
Group Comparison	**Incidence Rate Ratio (95% CI)**			**Incidence Rate Ratio (95% CI)**			**Incidence Rate Ratio (95% CI)**		
Healthy controls	3.02 (1.71-5.35)	<.001	89.8	NA	NA	NA	NA	NA	NA
Psychiatric controls	1.79 (1.31-2.44)	<.001	85.2	2.02 (1.42-2.87)	<.001	57.0	NA	NA	NA

Abbreviations: NA, not available; T2DM, type 2 diabetes mellitus.

[a] Antipsychotic-exposed youth include 185 105 patients and 863 type 2 diabetes mellitus events in the crude incidence analyses and 310 438 patient-years and 842 type 2 diabetes mellitus events in the incidence rate analysis.

[b] Healthy controls include 298 803 patients and 504 type 2 diabetes mellitus events in the crude incidence analyses and 463 084 patient-years and 504 type 2 diabetes mellitus events in the incidence rate analysis.

[c] Psychiatric controls include 1 342 121 patients and 3235 type 2 diabetes mellitus events in the crude incidence analyses and 2 071 135 patient-years and 3198 type 2 diabetes mellitus events in the incidence rate analysis.

[d] *P* values in the single-group analyses indicate that the rates are significantly different from zero (chance).

controls, with an unadjusted, cumulative risk of 2.61 (95% CI, 0.80-8.52) per 1000 patient-years and an incidence rate of 1.74 (95% CI, 1.10-2.38) per 1000 patient-years ($P < .001$ for both). The risk was lowest in healthy controls, with an unadjusted, cumulative risk of 2.15 (95% CI, 0.84-5.47) per 1000 patient-years and an incidence rate of 1.28 (95% CI, 0.78-1.79) per 1000 patient-years ($P < .001$ for both) (**Table 2**).

Subtracting the risk in psychiatric controls and healthy controls from that in antipsychotic-exposed youth, these numbers translate into an excess of 3.11 and 3.57 new T2DM cases per 1000 psychiatric controls and healthy controls, or an NNH of 322 and 280, respectively. With regard to the incidence, the numbers correspond to an excess of 1.35 and 2.41 T2DM cases per 1000 patient-years of antipsychotic exposure or follow-up compared with psychiatric controls and healthy controls, or an NNH of 740 or 398 per patient-year, respectively.

T2DM in Antipsychotic-Exposed Youth vs Psychiatric Controls and Healthy Controls

Compared with psychiatric controls, T2DM risk was significantly greater in antipsychotic-exposed youth compared with psychiatric controls, with an OR of 2.09 (95% CI, 1.50-2.90; $P < .001$) and an IRR of 1.79 (95% CI, 1.31-2.44; $P < .001$). In addition, T2DM risk was significantly greater in antipsychotic-exposed youth compared with healthy controls, with an OR of 2.58 (95% CI, 1.56-4.24; $P < .001$) and an IRR of 3.02 (95% CI, 1.71-5.35; $P < .001$) (Table 2). These findings were based on 8 studies (298 803 patients and 463 084 patient-years) (**Figure 1** and **Figure 2**). Furthermore, psychiatric controls had higher T2DM risk than healthy controls, with an OR of 1.57 (95% CI, 1.29-1.90; $P < .001$) and an IRR of 2.02 (95% CI, 1.42-2.87; $P < .001$) (Table 2).

No publication bias was identified for any of the comparisons ($P = .39$ to $P = .72$ for cumulative, unadjusted risk and $P = .26$ to $P = .91$ for incidence) (Egger regression test). In the antipsychotic-exposed youth vs psychiatric controls, the trim and fill method identified one missing study in the comparison of cumulative, unadjusted risk (adjusted OR, 1.96; 95% CI, 1.44-2.66; $P < .001$) and 2 missing studies in the comparison of the incidence (adjusted IRR, 1.51; 95% CI, 1.13-2.01; $P < .001$).

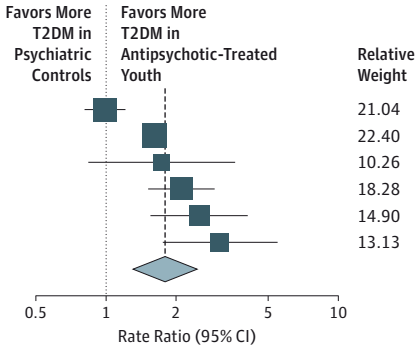
Sensitivity Analyses: Moderation of the Results by Precision of T2DM Definition and Study Quality

The results of the unadjusted, cumulative T2DM risk and incidence, as well as those of the group comparisons, were replicated independent of T2DM definition, the possibility of T1DM inclusion, or the potential inclusion of patients treated with oral antidiabetic medications for reasons other than T2DM. These results are summarized in **Figure 3** and in eTable 3 and eTable 4 in the Supplement.

Studies that potentially included T1DM cases yielded significantly higher "T2DM" incidence rates per patient-year than those that did not ($P = .03$). Conversely, the unadjusted, cumulative risk and all group comparisons were unaffected by this T2DM definition. Study quality, measured with the NOS, was not associated with the unadjusted, cumulative T2DM risk ($P = .19$) or exposure-adjusted T2DM incidence rate ($P = .67$) (eTable 1 in the Supplement).

Figure 1. Forest Plot of Incidence Rate Ratio for T2DM per Patient-Years in Antipsychotic-Exposed Youth vs Psychiatric Controls

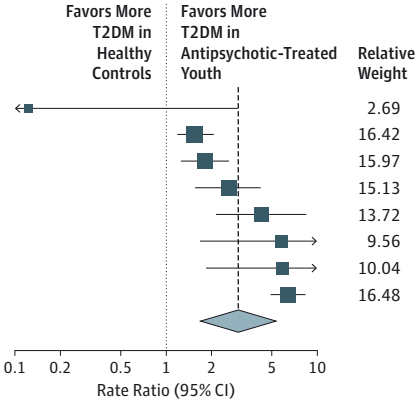
Source	Statistics for Each Study: Rate Ratio (95% CI)	Z-Value	P Value	No. With Diabetes/Total No.: Antipsychotic-Exposed Youth	Psychiatric Controls
McIntyre and Jerrell,[48] 2008	0.987 (0.810-1.202)	-0.130	.90	125/36 473	469/135 072
Rubin et al,[54] 2015	1.600 (1.440-1.778)	8.753	<.001	401/171 185	2563/1 750 722
Andrade et al,[34] 2011	1.742 (0.845-3.588)	1.505	.13	12/3710	19/10 231
Nielsen et al,[51] 2014	2.117 (1.523-2.943)	4.463	<.001	52/32 647	111/147 539
Enger et al,[47] 2013	2.519 (1.562-4.064)	3.786	<.001	71/12 309	22/9608
Bobo et al,[35] 2013	3.105 (1.769-5.447)	3.949	<.001	92/38 022	14/17 963
Total	1.791 (1.312-2.445)	3.672	<.001		



T2DM indicates type 2 diabetes mellitus.

Figure 2. Forest Plot of Incidence Rate Ratio for T2DM per Patient-Years in Antipsychotic-Exposed Youth vs Healthy Controls

Source	Statistics for Each Study: Rate Ratio (95% CI)	Z-Value	P Value	No. With Diabetes/Total No.: Antipsychotic-Exposed Youth	Healthy Controls
Arango et al,[46] 2014	0.123 (0.005-3.030)	-1.281	.200	1/136	0/6
McIntyre and Jerrell,[48] 2008	1.560 (1.185-2.055)	3.165	.002	125/36 473	85/38 700
Morrato et al,[50] 2010	1.812 (1.260-2.605)	3.207	.001	48/2648	74/7397
Sohn et al,[55] 2015	2.574 (1.568-4.228)	3.736	<.001	27/8161	37/28 792
Andrade et al,[34] 2011	4.249 (2.144-8.421)	4.145	<.001	12/3710	26/34 156
Liao et al,[52] 2011 (SGA)	5.774 (1.690-19.725)	2.797	.005	4/1755	7/17 734
Liao et al,[52] 2011 (FGA)	5.889 (1.847-18.775)	2.997	.003	4/2835	10/41 735
Enger et al,[47] 2013	6.412 (4.934-8.331)	13.904	<.001	71/12 309	265/294 564
Total	3.019 (1.703-5.351)	3.783	<.001		



FGA indicates first-generation antipsychotic; SGA, second-generation antipsychotic; and T2DM, type 2 diabetes mellitus.

Moderation by Age: Samples With Patients 18 Years or Younger Only

The results for the unadjusted, cumulative risk, for the incidence, and for the group differences were replicated when excluding studies with patients older than 18 years. The mean age of the study samples did not significantly moderate the unadjusted, cumulative T2DM risk ($P = .31$) or T2DM incidence ($P = .43$).

Mediation by Follow-up Time

Increased T2DM risk with antipsychotic treatment was mediated by longer follow-up duration ($P < .001$). Conversely, study follow-up duration did not mediate T2DM incidence ($P = .47$), which was already adjusted for patient-years.

Multivariable Model

In the multivariable meta-regression model pooling all SGAs together, only longer follow-up duration emerged as a significant mediating variable of cumulative T2DM risk in antipsychotic-exposed youth ($r^2 = 0.70$, $P < .001$) (eTable 5 in the Supplement). When entering individual SGAs separately, greater T2DM risk was associated with longer follow-up duration ($P < .001$), olanzapine prescription ($P < .001$), and male sex ($P = .002$) (10 studies, $r^2 = 1.00$, $P < .001$) (eTable 6 in the Supplement).

Pooling SGAs together, greater T2DM incidence was associated with SGA prescription ($P \leq .05$), whereas autism spectrum disorder diagnosis ($P = .048$) was associated with lower T2DM incidence (13 studies, $r^2 = 0.21$, $P = .04$) (eTable 7 in the Supplement). When entering individual SGAs separately to the model, no significant moderators emerged for T2DM incidence.

Correlates of T2DM Incidence Identified in Published Studies

Demographics

The findings regarding the influence of sex and age on T2DM risk during antipsychotic treatment have been inconsistent.[35,48,50-52] These results are summarized in eTable 8 in the Supplement.

Diagnosis

One study[35] showed a significantly elevated risk for patients with BPD and either conduct disorder or ADHD. Other diagnoses associated with T2DM were autism, DBD, and mood disorders,[34] while one study[51] did not find any significant effects of psychiatric diagnoses on the risk of or time until developing T2DM using multivariable analyses (eTable 8 in the Supplement).

Figure 3. Subgroup Analyses: Unadjusted, Cumulative Risk, and Incidence

Healthy Controls vs Antipsychotic-Treated Youth

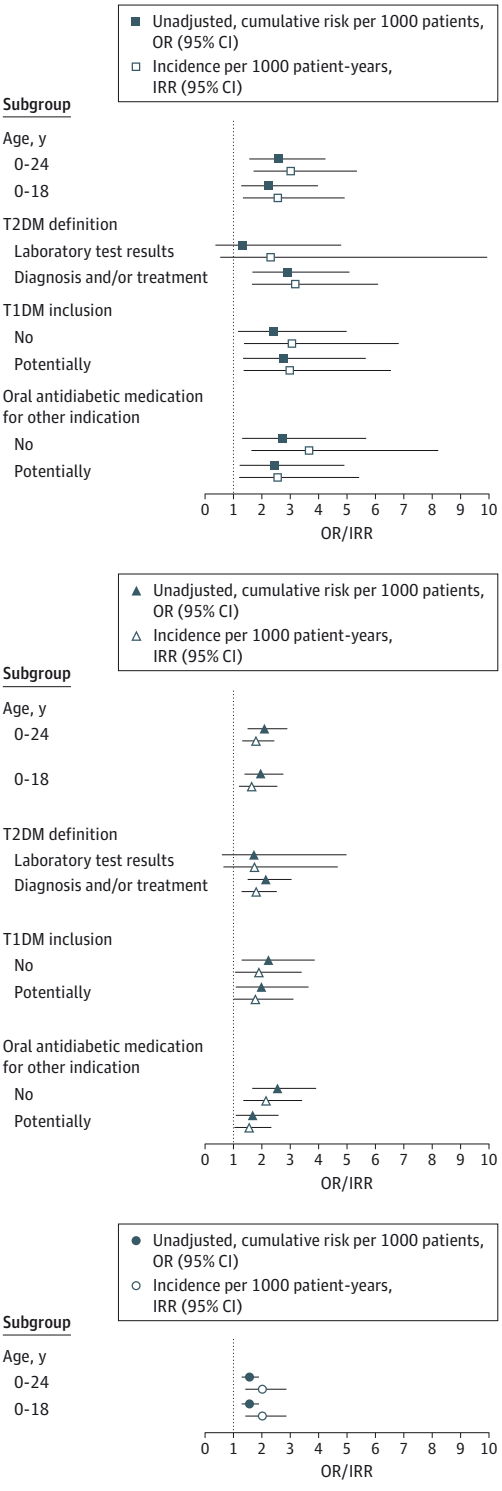
Healthy Controls			Antipsychotic-Treated Youth				
No.	Patient-Years	T2DM Cases	No.	Patient-Years	T2DM Cases	OR (95% CI)	IRR (95% CI)
298803	463084	504	37999	68028	292	2.58 (1.56-4.24)	3.02 (1.71-5.35)
268923	403615	487	35011	63438	284	2.25 (1.28-3.95)	2.56 (1.34-4.92)
38559	43161	26	9915	3846	13	1.33 (0.37-4.79)	2.31 (0.54-9.93)
260244	428922	478	28084	64182	279	2.92 (1.67-5.09)	3.18 (1.66-6.10)
56460	126961	139	13364	49224	160	2.75 (1.34-5.66)	2.99 (1.36-6.55)
242343	336123	365	24635	18803	132	2.40 (1.16-4.99)	3.06 (1.37-6.82)
56475	126967	139	13643	49361	161	2.45 (1.22-4.91)	2.56 (1.20-5.43)
242328	336117	365	24356	18667	131	2.72 (1.31-5.67)	3.67 (1.64-8.21)

Psychiatric Controls vs Antipsychotic-Treated Youth

Psychiatric Controls			Antipsychotic-Treated Youth				
No.	Patient-Years	T2DM Cases	No.	Patient-Years	T2DM Cases	OR (95% CI)	IRR (95% CI)
1342121	2071135	3235 (3198)	169840	294347	74 (753)	2.09 (1.50-2.90)	1.79 (1.31-2.44)
1327692	2053172	3221 (3184)	140982	256325	682 (661)	2.00 (1.39-2.76)	1.64 (1.20-2.55)
26265	10231	19	9636	3710	12	1.72 (0.60-4.98)	1.74 (0.65-4.68)
1315856	2060904	3216 (3179)	160204	290637	762 (741)	2.14 (1.50-3.05)	1.80 (1.29-2.53)
71213	300574	594	13417	107143	269	1.99 (1.08-3.65)	1.77 (1.01-3.11)
1270908	1770561	2641 (2604)	129589	187204	505 (484)	2.23 (1.29-3.86)	1.90 (1.06-3.40)
1251601	1903757	3046	140549	245681	618	1.68 (1.08-2.59)	1.56 (1.04-2.34)
90520	167378	189 (152)	29291	48666	156 (135)	2.55 (1.66-3.92)	2.15 (1.35-3.42)

Healthy Controls vs Psychiatric Controls

Healthy Controls			Psychiatric Controls				
No.	Patient-Years	T2DM Cases	No.	Patient-Years	T2DM Cases	OR (95% CI)	IRR (95% CI)
231828	267429	376	23126	52492	376	1.57 (1.29-1.90)	2.03 (1.42-2.87)
231828	267429	376	23126	52492	376	1.57 (1.29-1.90)	2.03 (1.42-2.87)



The T2DM cases in parentheses indicate the number of cases per patient-years if different from T2DM cases per number of patients (data missing of one study[53]). IRR indicates incidence rate ratio; OR, odds ratio; T1DM, type 1 diabetes mellitus; and T2DM, type 2 diabetes mellitus.

Antipsychotic Medication, Dosage, and Exposure Time

One study[47] found an elevated T2DM risk when comparing SGAs vs FGAs (hazard ratio, 3.39, 95% CI, 0.83-13.90), while another study[35] found an elevated risk when restricting the cohort to SGA users. Conversely, 2 single cohorts (each receiving either FGAs or SGAs) had similar T2DM risk.[52]

In 2 studies,[35,54] ziprasidone hydrochloride or aripiprazole was associated with higher T2DM risk compared with other SGAs (eTable 5 in the Supplement). Lower T2DM risk was reported for aripiprazole in another study.[48] Furthermore, clozapine[51] and antipsychotic polypharmacy[48] were associated with significantly increased T2DM risk.

The T2DM risk did not vary significantly by baseline antipsychotic dosage but increased with cumulative dose of all antipsychotics, especially with risperidone and in children 6 to 17 years old.[35] No significant dosage-associated risk was found in another study[51] using defined daily dose instead of the actual mean daily dose. Whereas one study[35] reported an increased T2DM risk within the first year of antipsychotic exposure (which was sustained for ≥1 year even after antipsychotic treatment discontinuation), another study[54] did not find a significant effect of antipsychotic exposure time on T2DM risk.

Coprescribed Medication

Effects of coprescribed medications on T2DM risk were reported in only 2 studies.[35,54] One study[54] indicated an increased T2DM risk with adjunctive antidepressant use, whereas the results were inconsistent regarding adjunctive stimulant treatment in both studies.

Glucose Level Screening

One study[35] demonstrated an increased T2DM risk related to glucose level screening. This result was found both for antipsychotic users who did or did not have a glucose level screening at baseline or during the follow-up period.

Discussion

This meta-analysis of T2DM risk in antipsychotic-exposed youth indicates that the unadjusted, cumulative T2DM risk and incidence of T2DM, respectively, were 2.6-fold and 3.0-fold higher compared with healthy controls and 2.1-fold and 1.8-fold higher compared with psychiatric controls. The attenuated difference compared with psychiatrically ill youth reflects that unhealthy lifestyle behaviors and other pharmacological treatments associated with psychiatric disorders likely also contribute to the risk of weight gain or obesity, metabolic abnormalities, and T2DM. For example, BPD and depression, as well as mood stabilizers and antidepressants, have been associated with metabolic syndrome and T2DM.[33,56-59] Accordingly, T2DM risk was also 1.5-fold and 2.0-fold higher in psychiatrically ill youth not exposed to antipsychotics compared with healthy controls.

Although the T2DM risk was significantly higher in antipsychotic-exposed youth than in psychiatric controls and healthy controls, the number of actual excess cases was low, at least during the mean (SD) follow-up of 1.7 (2.3) years (range, 0.38-8.81 years). Nevertheless, the clinical importance of these findings is underscored by studies[60,61] showing increased morbidity and mortality associated with an earlier T2DM onset. The relevance of our findings is further underscored by the fact that T2DM is only the most severe outcome of an interplay between antipsychotic exposure and genetic and lifestyle factors that lead to obesity and insulin resistance, which in and of themselves have serious health risks, especially when starting early in life.[16,18-22,60,61] Our meta-analysis identified 3.1 and 3.6 excess T2DM cases per 1000 psychiatric controls and healthy controls, respectively, as well as an excess of 1.4 and 2.4 T2DM cases per 1000 patient-years of antipsychotic exposure or follow-up compared with psychiatric controls and healthy controls, respectively. This increased risk must be balanced carefully against the potential benefits of antipsychotics[4-6,9,15,17,26] and underscores the need for prescribers to exhaust lower-risk treatment alternatives before initiating antipsychotic treatment and to routinely monitor youth for weight gain and metabolic abnormalities.

Caution should be especially high in patients with nonpsychotic disorders, in whom clinicians should aim for the shortest necessary treatment duration. This caveat is underscored by the fact that follow-up and thereby treatment duration increased T2DM risk.

In multivariable analyses, T2DM risk was significantly greater in male individuals than in female individuals, in youth treated with olanzapine, and in those with longer follow-up duration. The T2DM incidence was significantly greater in youth treated with SGAs but was lower in youth with autism spectrum disorder. The greater risk for T2DM in male individuals is consistent with data in adults.[16,60] Our results confirm that T2DM risk with SGAs is not homogeneous and that olanzapine treatment is a major modifiable risk factor. Whether the lower risk in youth with autism spectrum disorder is driven by other diagnostic groups that are associated with a higher T2DM risk (eg, mood or psychosis spectrum disorders) or by comedications used for these patients[31,33,34,56,59,62] requires further clarification. Study quality assessed with the NOS did not significantly affect the findings. Although not all aspects of study quality are covered by the criteria in the NOS, many of those relevant to the study of T2DM were captured by the additional subgroup and sensitivity analyses, which confirmed the overall results.

In patient-level analyses of T2DM risk factors conducted in the original studies, youth in mid to late adolescence seemed to have a greater T2DM risk, likely due to longer antipsychotic exposure or puberty-related insulin resistance.[63] The results regarding sex-related risk remained inconclusive. Youth with mood disorder diagnoses seemed to have a higher risk of antipsychotic-related T2DM than youth with other diagnoses (eg, autism spectrum disorder), which is consistent with the findings of our meta-regression analysis. Other risk factors included antidepressant cotreatment, consistent with elevated T2DM risk compared with healthy controls in antidepressant-treated youth,[34] as well as cumulative antipsychotic duration and dose and antipsychotic cotreatment, likely related to greater medication exposure and illness severity. Finally, in one study,[54] aripiprazole was associated with a significantly higher T2DM risk than risperidone, with an additional, trend-level higher risk for ziprasidone. Because both aripiprazole and ziprasidone have the lowest risk of weight gain and metabolic abnormalities in youth in prospective investigations,[16] these database study findings are likely owing to the increased

likelihood that higher-risk patients or those with concerning cardiometabolic adverse effects due to other antipsychotics are being started on or switched to these 2 lower-risk antipsychotics. This hypothesis is supported by a large Danish registry study[51] of 7139 antipsychotic-naive patients followed up for 6.6 years in which aripiprazole was associated with a reduced T2DM risk, while olanzapine (as in our meta-regression analysis and in most prospective studies[16,18,19,21]) and low-potency FGAs and clozapine were associated with an elevated T2DM risk.[31] Because all but one study[23] (which focused on olanzapine treatment only) reported on naturalistic settings with a range of antipsyhotics, a detailed comparison of different antipsychotics was not possible in this meta-analysis.

The results of this meta-analysis need to be interpreted within several limitations. First, although we were able to meta-analyze 13 studies with 185 105 antipsychotic-exposed youth, the main limitations are few studies with data on T2DM risk and the short and heterogeneous mean follow-up duration of 1.7 years (range, 0.38-8.81 years). Second, identified studies were heterogeneous regarding design, patient ascertainment, sample characteristics, assessments, outcomes, and matching procedures compared with the control groups, likely contributing to heterogeneity of the results. For example, retrospective database studies and prospective, observational, or open-label studies were combined. While this choice increased heterogeneity, both study types have their strengths and weaknesses, which are complementary, with higher generalizability of the samples in the database studies but greater granularity of the assessments and precision T2DM definitions in the prospective studies. However, although the findings were heterogeneous, subgroup and sensitivity analyses replicated the overall results, indicating that the effect size estimates varied within the significantly greater T2DM risk range and not between significant and nonsignificant results. Moreover, the results were unaffected by study quality, which generally was high. Third, there are several restrictions because of the naturalistic setting in all but one study[23] (which focused on olanzapine treatment only), as well as the fact that data of all but 3 studies[23,46,49] were collected retrospectively. Consequently, the results might have been affected by the following factors: (1) part of the follow-up period could have occurred after stopping antipsychotic treatments, resulting in a conservative T2DM risk estimate associated with antipsychotic use in youth; (2) metabolically higher-risk youth might be channeled to lower-risk medication (channeling bias); (3) generally, low glucose level testing rates in youth receiving antipsychotics[64,65] may have resulted in undetected T2DM cases (surveillance bias),[66] adding to the conservative bias of the results and requiring additional studies with adequate glucose level monitoring; and (4) cases reported as T2DM might have been incorrectly classified (eg, by the counting of T1DM or other illnesses for which antidiabetic medication was prescribed [misclassification bias]), leading to potentially inflated outcomes. However, these biases appear to have been small because they did not significantly affect the overall results when conducting subgroup and sensitivity analyses. Moreover, the different T2DM definitions that can lead to an inflated rate or to a deflated rate affected the comparison groups equally. Fourth, although schizophrenia spectrum disorders have been associated with T2DM development,[62,67,68] too few antipsychotic-exposed youth had such disorders to enable meaningful subgroup or meta-regression analyses. Fifth, because long-term follow-up studies of antipsychotic-exposed youth for T2DM (which is a distal and low-rate adverse effect) are difficult to conduct,[69] all but 2 studies were observational, database studies, restricting the available data. For example, much potentially relevant data on T2DM-related variables were missing in the databases (eg, family history of T2DM, body mass index, smoking status, diet and exercise behaviors, and illness severity) and were therefore not available for confounding adjustment. Because T2DM is a long-term adverse effect that is related to treatment, illness, behavioral, genetic, and environmental factors, more prospective, long-term observational studies of youth treated with antipsychotics are needed that assess relevant risk factors for T2DM beyond antipsychotic treatment.

Conclusions

The results of this meta-analysis indicate an association between antipsychotic treatment and increased risk for the development of T2DM in youth. These risks should be considered in the clinical risk-benefit evaluation when initiating or continuing antipsychotic treatment in this age group. Although the absolute incidence rates are small (at least during a mean follow-up period of 1.7 years), antipsychotics should only be used when lower-risk interventions have failed, and differential tolerability profiles should influence the antipsychotic choice, including avoidance of olanzapine.[18,19,21,70] Antipsychotics should be used judiciously and for the shortest necessary duration. Furthermore, routine and proactive monitoring of cardiovascular risk factors should be enforced when prescribing antipsychotics to youth. Patients and their caregivers also need to be informed about possible adverse effects and supported in alleviating cardiometabolic risk via healthy nutrition and physical activities.[18,27,71-74]

ARTICLE INFORMATION

Correction: This article was corrected on March 2, 2016, to fix an error in author affiliations.

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Acquisition, analysis, or interpretation of data: Galling, Roldán, R. E. Nielsen, J. Nielsen, Gerhard, Carbon, Stubbs, Vancampfort, De Hert, Olfson, Kahl, Martin, Guo, Lane, Sung, Liao, Arango, Correll.
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