Association of Selective Serotonin Reuptake Inhibitors With the Risk of Type 2 Diabetes in Children and Adolescents

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**IMPORTANCE** Concerns exist that use of selective serotonin reuptake inhibitors (SSRIs) increases the risk of developing type 2 diabetes (T2D) in adults, but evidence in children and adolescents is limited. In the absence of a randomized clinical trial, evidence must be generated using real-world data.

**OBJECTIVE** To evaluate the safety of SSRI use in children and adolescents with respect to the associated risk of T2D.

**DESIGN, SETTING, AND PARTICIPANTS** This cohort study of patients aged 10 to 19 years with a diagnosis for an SSRI treatment indication was conducted within the nationwide Medicaid Analytic eXtract (MAX; January 1, 2000, to December 31, 2014) and the IBM MarketScan (January 1, 2003, to September 30, 2015) databases. Data were analyzed from November 1, 2018, to December 6, 2019.

**EXPOSURES** New users of an SSRI medication and comparator groups with no known metabolic adverse effects (no antidepressant exposure, bupropion hydrochloride exposure, or psychotherapy exposure). Within-class individual SSRIs were compared with fluoxetine hydrochloride.

**MAIN OUTCOMES AND MEASURES** Incident T2D during follow-up. Intention-to-treat effects were estimated using Cox proportional hazards regression models, adjusting for confounding through propensity score stratification. As-treated effects to account for continuous treatment were estimated using inverse probability weighting and marginal structural models.

**RESULTS** A total of 1,582,914 patients were included in the analysis (58.3% female; mean [SD] age, 15.1 [2.3] years). The SSRI-treated group included 316,178 patients in the MAX database (publicly insured; mean [SD] age, 14.7 [2.1] years; 62.2% female) and 211,460 in the MarketScan database (privately insured; mean [SD] age, 15.8 [2.3] years; 63.9% female) with at least 2 SSRI prescriptions filled, followed up for a mean (SD) of 2.3 (2.0) and 2.2 (1.9) years, respectively. In publicly insured patients, initiation of SSRI treatment was associated with a 13% increased hazard of T2DM (intention-to-treat adjusted hazard ratio [aHR], 1.13; 95% CI, 1.04-1.22) compared with untreated patients. The association strengthened for continuous SSRI treatment (as-treated aHR, 1.33; 95% CI, 1.21-1.47), corresponding to 6.6 (95% CI, 4.2-10.4) additional cases of T2D per 10,000 patients treated for at least 2 years. Adjusted HRs were lower in privately insured patients (intention-to-treat aHR, 1.01 [95% CI, 0.84-1.23]; as-treated aHR, 1.10 [95% CI, 0.88-1.36]). Findings were similar when comparing SSRI treatment with psychotherapy (publicly insured as-treated aHR, 1.44 [95% CI, 1.25-1.65]; privately insured as-treated aHR, 1.21 [95% CI, 0.93-1.57]), whereas no increased risk was observed compared with bupropion treatment publicly insured as-treated aHR, 1.01 [95% CI, 0.79-1.29]; privately insured as-treated aHR, 0.87 [95% CI, 0.44-1.70]). For the within-class analysis, no medication had an increased hazard of T2D compared with fluoxetine.

**CONCLUSIONS AND RELEVANCE** These findings suggest that children and adolescents initiating SSRI treatment may be at a small increased risk of developing T2D, particularly publicly insured patients. The magnitude of association was more modest than previously reported, and the absolute risk was small. The potential small risk should be viewed in relation to the efficacy of SSRIs for its major indications in young patients.
Children and adolescents taking selective serotonin reuptake inhibitors (SSRIs) should be closely monitored, given the potential adverse effects.1,3 Despite these concerns, SSRI use in young patients remains widespread, given the increasing prevalence of depression in this population4-8 and the efficacy of SSRIs for pediatric depression and anxiety disorders.9,10 In 2012, an estimated 3.5% of children (aged 10-14 years) and 6.2% of adolescents (aged 15-19 years) in the United States were taking an antidepressant, with 72% of these patients treated with an SSRI.8

An association between SSRIs and type 2 diabetes (T2D) has been reported in several studies conducted in adults.11-18 Although residual biases could not be excluded as alternative explanations,19-22 weight gain is a potential biological mechanism. Selective serotonin reuptake inhibitors are generally associated with modest weight gain,23-25 but this may be sufficient in transitioning some patients from normal weight to overweight/obesity and elevate the risk of T2D.26 Evidence regarding this potential safety concern in children and adolescents is limited.26,27 A recent observational study26 found that treatment with SSRIs or serotonin and norepinephrine reuptake inhibitors may be associated with a 90% increased risk of T2D in youths (aged 5-20 years). However, this study was not sufficiently large to examine the SSRI class alone or specific SSRIs, which is needed to inform clinical decision-making, because weight gain and metabolic adverse effects differ by class and for individual drugs within the same class.25 Furthermore, it is possible that behaviors associated with depression severity may have contributed to the observed risk.28-30 More evidence is needed, given the widespread prescription of SSRIs and potential health threats posed by T2D onset during childhood and adolescence.31

Children and adolescents are often excluded from randomized clinical trials (RCTs), resulting in a lack of evidence on medication safety and widespread off-label prescribing.32-41 Rapid changes in growth during childhood and adolescence can alter drugs’ pharmacokinetics and pharmacodynamics, so high-quality age-specific drug safety data are needed to inform prescribing decisions.32 Because it is unlikely that a sufficiently large RCT will be conducted to study SSRIs and T2D in young patients, evidence must be generated using real-world data.33,42,43 Using data from 2 nationwide health care databases, we conducted a cohort study of children and adolescents to examine the association between SSRIs and T2D, with careful control for potential biases.

Methods

Study Population

This study leveraged nationwide US claims data from the Medicaid Analytic eXtract (MAX; January 1, 2000, to December 31, 2014) database, consisting of patients enrolled in Medicaid and the Children’s Health Insurance Program, and IBM MarketScan (MarketScan; January 1, 2003, to September 30, 2015) database, consisting of privately insured patients. Within these databases, we identified patients aged 10 to 19 years with a diagnosis for an SSRI indication (ie, depression, generalized or social anxiety disorder, obsessive-compulsive disorder, post-traumatic stress disorder, panic disorder, or bulimia nervosa) (eTable 1 in Supplement). The research was approved by the institutional review board of Brigham and Women’s Hospital, which granted a waiver of informed consent for the use of deidentified data. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Exposure

The exposed group consisted of new users of an SSRI (eTable 2 in the Supplement). The index date was defined as the date of the first observed SSRI dispensing. Patients without continuous enrollment and those with evidence of antidepressant use, diabetes-related conditions, pregnancy, hospice care, or serious medical conditions during the 365 days before the index date were excluded (eTable 1 in the Supplement).

We compared patients who initiated SSRI treatment with patients who had a diagnosis for an SSRI indication but no antidepressant exposure (untreated group). At the time of each SSRI user’s index date, we randomly selected 2 untreated patients who had at least 1 medical encounter within 14 days before or after the index date and were the same age. The untreated patient’s index date was the medical encounter date. In secondary analyses, 2 active comparators with no known metabolic adverse effects were used to further reduce the risk of confounding by the indication or its severity.45,46 Specifically, we identified new users of bupropion hydrochloride, an antidepressant known to not result in weight gain,23,24,47 and new users of psychotherapy. The index dates were defined as the date of the first bupropion dispensing and the first health care claim for psychotherapy, respectively. Patients were required to satisfy the previously outlined inclusion and exclusion criteria.

We also compared the individual SSRI medications (within-class comparison).51 Patients receiving fluoxetine hydrochloride served as the reference group.51,49 Classification of patients into treatment groups (citalopram hydrobromide, escitalopram oxalate, fluoxetine, fluvoxamine maleate, paroxetine hydrochloride or paroxetine mesylate, and sertraline hydrochloride) was based on the index dispensing.
Outcome
Patients were followed up until the first diagnosis of T2D. Cases were identified using a validated algorithm developed to identify T2D in children based on administrative data (sensitivity, 90.3%; specificity, 95.0%). This definition was based on the presence of inpatient or outpatient diagnoses for T2D and use of antidiabetic medications. Patients were censored at the time of other diabetes-related medical encounters (type 1, gestational, and secondary diabetes), hospice care, pregnancy, end of insurance coverage, or end of available data.

Covariates
Baseline characteristics were measured during the 365 days before the index date. More than 100 covariates were selected a priori as plausible confounders or proxies of confounders. These include demographic characteristics, psychiatric diagnoses, metabolic conditions, concomitant medications, and use of health care services (eTable 3 in the Supplement).

Intention-to-Treat Analysis
To minimize exposure misclassification, the intention-to-treat (ITT) analysis was restricted to patients with at least 1 additional SSRI prescription during the 180 days after the index dispensing (exposure assessment period). Untreated patients were required to have no antidepressant prescriptions and at least 1 additional medical encounter during the exposure assessment period. Active comparators were similarly constructed (eFigure 1 in the Supplement). Patients with the outcome or a censorship event during the exposure assessment period were excluded. Follow-up began the 181st day after the index date. Consistent with an ITT approach, we disregarded treatment changes during follow-up.

To adjust for baseline confounding, we used propensity score stratification. After trimming observations from the non-overlapping regions of the propensity score distribution, we constructed 10 propensity score strata based on the SSRI group’s propensity-score distribution. Within the strata of propensity score, patients in the comparator group were weighted according to the distribution of the SSRI exposed.54 Cox proportional hazards regression models were used to estimate hazard ratios (HRs) and 95% CIs.

As-Treated Analysis
An as-treated analysis was conducted to estimate the association of continuous SSRI treatment (vs untreated, bupropion treatment, and psychotherapy). For each 3-month window of follow-up (after the index date), we assessed whether patients remained adherent to their index exposure group. Specifically, SSRI and bupropion users were required to have a supply of at least 30 days for the respective treatment, and untreated patients and those receiving psychotherapy were required to remain free of antidepressant exposure. Patients were censored at the end of the 3-month window during which they no longer satisfied the definition for their baseline treatment group (ie, discontinued), initiated use of a different antidepressant, or had a previously described study censorship event. This analysis had a maximum 5-year observation period, because few patients remained in the risk set beyond that point.

Inverse probability of treatment weights, estimated using baseline covariates, were used to account for baseline confounding. Inverse probability of censoring weights, estimated as a function of baseline and time-varying covariates (updated every 3 months), were used to adjust for confounding and selection bias due to censoring.52,53 Weights were truncated at the 1st and 99th percentiles to prevent outliers from affecting the analysis. Pooled logistic marginal structural models were used to estimate HRs, and robust variance estimators were used to compute 95% CIs.54,55 In sensitivity analyses, we considered different approaches to modeling and truncating weights.

Subgroup and Sensitivity Analyses
Several subgroup and sensitivity analyses were conducted to evaluate the robustness of our primary results (between-class) in the ITT population. To explore potential effect modification, subgroup analyses were conducted separately for age (10-14 and 15-19 years), sex (female and male), and race/ethnicity (non-Hispanic White, Black, Hispanic/Latino, and other [MAX database only]). Additional subgroups were restricted to depression and anxiety diagnoses (the most common SSRI indications), excluded antipsychotic users (risk factor for T2D),56,57 and were restricted to stimulant users (could limit weight gain).58

In sensitivity analyses, the high-dimensional propensity score was used to account for proxies of unmeasured confounding.59,60 In negative control analyses, we examined the associations between SSRIs and incidence of hyperlipidemia and asthma. Control outcomes were selected a priori as outcomes that should have no association with SSRIs but may have a similar structure of confounding or a similar potential for detection bias as T2D. A null finding would provide indirect evidence of no substantial residual confounding or detection bias.61

We also conducted sensitivity analyses to explore potential residual confounding by obesity, which is poorly captured in administrative data but could be an important confounder, because adolescents with more severe depression are more likely to receive SSRIs, to have overweight/obesity, and to develop T2D.39,30,62,63 For a subset of the MAX population, body mass index data were obtained by linking their claims data to the Partners Healthcare Research Patient Data Registry, an electronic health record database consisting of patients who receive care in the Partners hospital systems in Massachusetts. Details are given in the eMethods in the Supplement.

Data were analyzed from November 1, 2018, to December 6, 2019. All analyses were conducted using SAS, version 9.4 (SAS Institute Inc).

Results

Patient Characteristics
A total of 1 582 914 patients were included in the primary ITT analysis (58.3% female; 41.7% male; mean [SD] age, 15.1 [2.3] years). The ITT cohort included 316 178 patients who initiated SSRI treatment and 632 356 age-matched untreated patients in the MAX database (publicly insured) and 211 460 patients who initiated SSRI treatment and 422 920 age-matched untreated...
patients in the MarketScan database (privately insured). The as-treated cohort was larger (≥2 prescriptions not required), with 439,205 SSRI-treated and 878,410 age-matched untreated publicly insured patients and 269,762 SSRI-treated and 539,524 age-matched untreated privately insured patients.

The SSRI-treated patients were more likely to be female (62.9%) and white (61.8%) (publicly insured only). They also had more medical diagnoses and medication use for both psychiatric-related and unrelated conditions (eg, 10.5% SSRI-treated vs 7.3% untreated had a diagnosis of bipolar disorder; 11.0% SSRI-treated vs 7.3% untreated filled a prescription for antipsychotics). Markers for obesity and metabolic conditions were similar between treated and untreated patients. After propensity-score stratification, all baseline characteristics were balanced across treatment groups, with absolute standardized differences of less than 0.10 (Table 1 and eTables 4 and 5 in the Supplement).64 Use of active comparators (bupropion and psychotherapy) also achieved balance in characteristics (eTables 6-9 in the Supplement).

In the ITT cohort, patients who initiated SSRI treatment were followed up for a mean (SD) of 2.3 (2.0) years in the publicly insured and 2.2 (1.9) years in the privately insured cohorts. Mean (SD) follow-up was shorter in the as-treated population (SSRI treated: 1.0 [1.0] years in publicly insured cohort and 1.1 [1.1] years in privately insured cohort) (Table 2 and eTable 10 in the Supplement).

**Between-Class and Within-Class Comparisons**

In publicly insured patients, the unadjusted incidence rate of T2D was 2.32 cases per 1000 person-years among patients who initiated SSRI treatment and 1.65 cases per 1000 person-years among untreated patients in the ITT population (Table 2). Unadjusted HRs in ITT analyses suggested an association between SSRI initiation and T2D compared with noninitiators (crude HR, 1.39; 95% CI, 1.31–1.49). After fully adjusting for baseline covariates, the association moved toward the null (adjusted HR [aHR], 1.13; 95% CI, 1.04–1.22) (Figure 1 and eTable 11 in the Supplement). The magnitude of association increased for continuous SSRI treatment in as-treated analyses (aHR, 1.33; 95% CI, 1.21–1.47), which corresponded to an additional 6.6 (95% CI, 4.2–10.4) T2D cases per 10,000 patients continuously treated for at least 2 years (number needed to harm, 1515 patients treated for ≥2 years for 1 patient to develop T2D) and an additional 28.4 (95%, 16.0–46.3) T2D cases per 10,000 continuously treated for at least 5 years (number needed to harm, 352) (eTable 12 in the Supplement). The association did not manifest until more than 1 year of follow-up (Figure 2).

In privately insured patients, absolute rates in the ITT population were lower: 0.63 cases per 1000 person-years among patients who initiated SSRI treatment and 0.54 cases per 1000 person-years among untreated patients (Table 2). After adjustment, there was no increased hazard of T2D in ITT (aHR, 1.01; 95% CI, 0.84–1.23) and no meaningful increased hazard of T2D in as-treated analyses (aHR, 1.10; 95% CI, 0.88–1.36) (Figure 1 and eTable 11 in the Supplement). This point estimate corresponds to an additional 3.7 (95% CI, –3.2 to 15.5) cases per 10,000 continuously treated for at least 5 years (eTable 12 in the Supplement).

Using active comparators, no increased hazard was observed comparing SSRI treatment with bupropion treatment (publicly insured as-treated aHR, 1.01 [95% CI, 0.79–1.29]; privately insured as-treated aHR, 0.87 [95% CI, 0.44–1.70]) (eTable 13 in the Supplement), whereas an increased hazard was observed compared with psychotherapy (publicly insured as-treated aHR, 1.44 [95% CI, 1.25–1.65]; privately insured as-treated aHR, 1.21 [95% CI, 0.93–1.57]) (eTable 14 in the Supplement).

Within-class HRs did not vary substantially by individual SSRI medication (Figure 3 and eTable 15 in the Supplement).

**Subgroup and Sensitivity Analyses**

Overall, findings did not vary substantially across subgroups (Figure 1 and eTable 16 in the Supplement). Results remained consistent after using high-dimensional propensity-score adjustment. No increased risks were observed in asthma and hyperlipidemia control outcomes, providing indirect evidence of no residual biases (eTable 17 in the Supplement). In as-treated analyses, different approaches to modeling and truncating weights did not alter our findings (eTable 18 in the Supplement). In bias analyses to explore the effect of residual confounding due to poorly measured obesity, we found that better measurement of obesity would not have substantially altered our conclusions (eMethods, eTables 19-22, and eFigure 2 in the Supplement).

**Discussion**

Using nationwide data from 2 US health care databases, we observed a small increased risk of T2D associated with SSRI treatment in children and adolescents, particularly among publicly insured patients. This association was not apparent during the first year of treatment and strengthened slightly with longer follow-up. Within the SSRI class, no individual medication increased the risk of T2D compared with fluoxetine. Findings were generally consistent across subgroup and sensitivity analyses.

A previous study26 found that use of SSRIs or serotonin and norepinephrine reuptake inhibitors in Medicaid-insured youths was associated with a substantial increased risk of T2D (risk ratio, 1.88; 95% CI, 1.34–2.64), with the risk intensifying with longer duration (>150 days). Our study found an attenuated association among Medicaid-insured SSRI users after evaluating the SSRI class alone and using different techniques to control for confounding by indication (ie, restriction to patients with an SSRI indication, time-varying confounding adjustment when evaluating continuous treatment, active comparators). Furthermore, we expand the evidence base by examining privately insured SSRI users, who had no meaningful increased risk of T2D.

Although small RCTs of adults65,66 found that SSRI treatment does not impair glucose metabolism in the short term, SSRI-induced weight gain may be associated with transitioning patients with normal weight to overweight/obesity25 and thereby elevating their risk for T2D. Unfortunately, the association between SSRIs and weight gain could not be directly assessed in our data. The long-term metabolic effects of SSRI treatment remain poorly characterized, with mixed evidence
Table 1. Baseline Characteristics of Patients With SSRI Treatment and Without Antidepressant Treatment in the Intention-to-Treat Population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>MAX database (publicly insured)</th>
<th>IBM MarketScan database (privately insured)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted</td>
<td>Accounting for propensity score decileb</td>
</tr>
<tr>
<td></td>
<td>SSRI group (n = 316 178)</td>
<td>Untreated group (n = 632 356)</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>14.7 (2.1)</td>
<td>14.7 (2.1)</td>
</tr>
<tr>
<td>Female</td>
<td>197 022 (62.2)</td>
<td>345 820 (54.7)</td>
</tr>
<tr>
<td>Race/ethnicityc</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>195 863 (61.9)</td>
<td>297 791 (47.1)</td>
</tr>
<tr>
<td>Black</td>
<td>50 194 (15.9)</td>
<td>150 119 (23.7)</td>
</tr>
<tr>
<td>Hispanic/Latino</td>
<td>44 363 (14.0)</td>
<td>123 650 (19.6)</td>
</tr>
<tr>
<td>Other</td>
<td>25 758 (8.1)</td>
<td>60 796 (9.6)</td>
</tr>
<tr>
<td>Use of health care</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of distinct generic drugs, median (IQR)</td>
<td>4 (2-7)</td>
<td>3 (1-6)</td>
</tr>
<tr>
<td>No. of outpatient visits, median (IQR)</td>
<td>21 (15-31)</td>
<td>21 (15-31)</td>
</tr>
<tr>
<td>Any hospitalization</td>
<td>42 485 (13.4)</td>
<td>40 675 (6.4)</td>
</tr>
<tr>
<td>Mental health hospitalization</td>
<td>36 324 (11.5)</td>
<td>26 812 (6.4)</td>
</tr>
<tr>
<td>Medical diagnoses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>264 431 (83.5)</td>
<td>448 668 (71.0)</td>
</tr>
<tr>
<td>Generalized anxiety disorder</td>
<td>101 862 (32.2)</td>
<td>175 201 (27.7)</td>
</tr>
<tr>
<td>OCD</td>
<td>7620 (2.4)</td>
<td>6036 (1.0)</td>
</tr>
<tr>
<td>Psychotherapy</td>
<td>95 354 (30.1)</td>
<td>189 194 (29.9)</td>
</tr>
<tr>
<td>ADHD</td>
<td>64 614 (20.4)</td>
<td>114 487 (18.1)</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>39 650 (12.5)</td>
<td>55 753 (8.8)</td>
</tr>
<tr>
<td>Obesity</td>
<td>13 896 (4.4)</td>
<td>25 932 (4.0)</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>3548 (1.1)</td>
<td>6643 (1.1)</td>
</tr>
<tr>
<td>Smoking</td>
<td>5845 (1.8)</td>
<td>8911 (1.4)</td>
</tr>
<tr>
<td>Concomitant medications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>47 628 (15.0)</td>
<td>63 108 (10.0)</td>
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<tr>
<td>Stimulants</td>
<td>61 785 (19.5)</td>
<td>101 833 (16.1)</td>
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<td>Benzodiazepines</td>
<td>16 774 (5.3)</td>
<td>15 583 (2.5)</td>
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<tr>
<td>Anticonvulsants</td>
<td>24 405 (7.7)</td>
<td>44 386 (7.0)</td>
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<tr>
<td>Mood stabilizers</td>
<td>42 437 (1.1)</td>
<td>42 704 (1.1)</td>
</tr>
<tr>
<td>Opioids</td>
<td>73 779 (23.3)</td>
<td>123 233 (19.5)</td>
</tr>
</tbody>
</table>

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; IQR, interquartile range; MAX, Medicaid Analytic Xtract; NA, not applicable; OCD, obsessive-compulsive disorder; SSRI, selective serotonin reuptake inhibitor.

a Unless otherwise indicated, data are expressed as number (percentage) of patients. Percentages have been rounded and may not total 100.

b Patients in the nonoverlapping regions of the propensity score distribution were trimmed. Within each propensity score decile, the untreated were weighted using the distribution of the SSRI initiators. The exposed to untreated ratio is not exactly 1:2 because patients with the outcome or censorship event during the 180 days after index date were excluded, and this may have occurred in slightly different proportions across treatment groups.

c Race/ethnicity may be an important confounder and/or effect modifier and was classified based on information submitted to the Centers for Medicare & Medicaid Services by individual states from Medicaid applications. Race/ethnicity data are not available in the IBM MarketScan database.
Association of SSRIs With Risk of Type 2 Diabetes in Children and Adolescents

Metabolism is limited. We found a small increased risk of T2D in children and adolescents, evidence regarding SSRIs and glucose inhibitors.

Abbreviations: ITT, intention-to-treat; SSRIs, selective serotonin reuptake inhibitors.

The ITT population was restricted to patients with at least 2 SSRI prescriptions (exposed) or zero antidepressant prescriptions (unexposed) during the first 6 months after index date. Follow-up began 181 days after index date. Numbers reflect after restricting to first cohort entry. Exposed to untreated ratio is not exactly 1:2 because patients with the outcome or censorship event during the 180 days after index date were excluded, and this may have occurred in slightly different proportions across treatment groups.

In the as-treated population, patients were censored after treatment discontinuation.

Table 2. Unadjusted Absolute Rate of Type 2 Diabetes Among Children and Adolescents With SSRI Treatment and Without Antidepressant Treatment

<table>
<thead>
<tr>
<th>Exposure group</th>
<th>Medicaid Analytic eXtract database (publicly insured)</th>
<th>IBM MarketScan database (privately insured)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of patients</td>
<td>No. of events</td>
</tr>
<tr>
<td>ITT population*</td>
<td>281,832</td>
<td>1523</td>
</tr>
<tr>
<td>SSRIs</td>
<td>619,422</td>
<td>2117</td>
</tr>
<tr>
<td>No antidepressant exposure</td>
<td>878,410</td>
<td>1856</td>
</tr>
<tr>
<td>As-treated population*</td>
<td>439,205</td>
<td>573</td>
</tr>
<tr>
<td>SSRIs</td>
<td>281,832</td>
<td>832</td>
</tr>
<tr>
<td>No antidepressant exposure</td>
<td>619,422</td>
<td>1523</td>
</tr>
</tbody>
</table>

All estimates reflect the hazard of T2D among children and adolescents treated with SSRIs compared with those without antidepressant treatment. In the intention-to-treat (ITT) analysis, the graph shows results of the unadjusted analysis, the analysis partially adjusted for demographics (age, sex, and race for the Medicaid Analytic eXtract database only) and treatment indication, and the analysis fully adjusted for all baseline covariates. In the as-treated analysis, the graph shows the results of the unadjusted analysis, the analysis adjusted for all baseline covariates, and the analysis adjusted for all baseline and time-varying covariates. For subgroups, all estimates reflect the hazard of T2D among children and adolescents treated with SSRIs compared with those without antidepressant treatment, fully adjusted for all baseline covariates. Propensity score models were reestimated within each subgroup. HR indicates hazard ratio.

Regarding the association between antidepressants and T2D, insulin resistance, and intermediate markers of T2D, the literature is limited. In children and adolescents, evidence regarding SSRIs and glucose metabolism is limited. We found a small increased risk of T2D among publicly insured patients who initiated SSRI treatment. The association strengthened with longer treatment periods, but the magnitude was more modest than previously reported and substantially smaller than the risk associated with other known risk factors for T2D, such as obesity, race, and poverty (2- to 7-fold increased risk).
In intention-to-treat analyses, Kaplan-Meier curves were weighted by the inverse of the propensity score (estimated probability of initiation of selective serotonin reuptake inhibitor [SSRI] treatment conditional on baseline covariates). In as-treated analyses, survival probabilities were weighted by stabilized treatment and censoring weights based on baseline and time-varying covariates and standardized to the joint distribution of baseline covariates.

In intension-to-treat analyses, this potential small risk of T2D, along with other potential adverse effects of SSRIs such as nausea and sleep disturbances,2-71 should be weighed against the benefits of treating pediatric depression and anxiety disorders.9,10 Because the patients in our cohorts were free of T2D at baseline, our study does not inform the treatment of patients with established T2D.

Heterogeneity in point estimates was observed across data sources. This is not unexpected, because the data sources reflect different populations with different underlying risks for T2D, comparable to heterogeneity observed in stratified analyses in RCTs. The increased risk of T2D was observed in publicly insured patients who are of lower socioeconomic status and represent a population with greater overall medical burden, more comorbidities, and a higher prevalence of risk factors for T2D,72 whereas no meaningful increased risk was observed in privately insured patients. These findings highlight the value of examining results across different populations with different underlying risks. Patients with high-risk characteristics should be monitored more closely for glucose intolerance.

This study highlights the opportunities of using RWD to generate evidence on drug safety in children and adolescents. First, health care databases enabled large cohorts with sufficient power to examine the SSRI class and individual SSRI medications and to perform clinically relevant subgroup analyses. Second, the longitudinal nature of these databases provided a chance to evaluate the long-term effects of treatment and to capture the development of T2D.

Limitations
There are challenges to using RWD to evaluate drug safety, but approaches can be leveraged to improve its validity. First, as in all nonrandomized studies, we cannot rule out the possibility of residual confounding by unmeasured characteristics, such as control of baseline blood glucose levels. Several attempts were made to minimize this possibility, including use of active comparators, adjustment for at least 100 baseline covariates (including proxies for high blood glucose levels), further adjustment for time-varying confounding in as-treated analyses, and use of control outcomes. In addition, we con-
ducted sensitivity analyses in a claims- and electronic health records–linked subset and found that body mass index was well-balanced between treatment groups, reducing its potential for confounding. However, in this linked subset, the sample size was small for bupropion. The potential role of confounding by obesity on observed estimates was illustrated in Figure 2 in the Supplement.

Second, RWD studies need evidence of exposure and a highly specific outcome definition.73 To increase the likelihood that patients took their medication, we required at least 1 additional prescription within the first 6 months after treatment initiation in ITT analyses. We also conducted as-treated analyses, censoring patients when they no longer received refills. Outcome misclassification was minimized by using a validated definition with high sensitivity and specificity.50 Finally, point estimates varied across comparator groups. If we conducted an RCT, SSRI users would be compared with a placebo group. However, placebo groups are difficult to mimic in RWD,74 so we explored several options to broaden our understanding. A positive association was observed compared with the untreated and psychotherapy groups. However, untreated patients and those receiving psychotherapy likely differ from those who receive an antidepressant with respect to disease severity and other clinical factors. Compared with bupropion, for which confounding by indication may pose a lower threat to validity, we observed no increased risk. One additional explanation could be that patients with overweight/obesity were more likely to initiate bupropion treatment compared with other antidepressants.75 Given the lack of a known biological mechanism, further investigation is needed to explore the association between bupropion and T2D. Most importantly, across all comparisons, the magnitude of association was lower than initially reported, suggesting that the risk of T2D is less of a safety concern than previously proposed.

Conclusions
This cohort study found that treatment with SSRIs during childhood and adolescence may be associated with a small increased risk of T2D, particularly among publicly insured patients. The magnitude of association was more modest than previously reported, and the absolute risk was small, providing evidence that this safety concern is not as substantial as initially reported. This potential risk, which is much lower in magnitude than the other known risk factors for T2D, should be weighed against the known benefits and risks of SSRI treatment to help inform treatment decision making in the pediatric population.

Figure 3. Within-Class Analysis of the Association Between Medications in the Selective Serotonin Reuptake Inhibitor (SSRI) Class and Type 2 Diabetes

<table>
<thead>
<tr>
<th>SSRI medication</th>
<th>No. of patients</th>
<th>No. of events</th>
<th>Person-years</th>
<th>Crude HR (95% CI)</th>
<th>Adjusted HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram</td>
<td>44331</td>
<td>139</td>
<td>93099</td>
<td>1.04 (0.89-1.21)</td>
<td>1.02 (0.87-1.19)</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>39236</td>
<td>235</td>
<td>89737</td>
<td>1.08 (0.92-1.26)</td>
<td>1.00 (0.85-1.17)</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>1349</td>
<td>12</td>
<td>4505</td>
<td>1.00 (0.56-1.78)</td>
<td>1.20 (0.68-2.13)</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>29124</td>
<td>155</td>
<td>78262</td>
<td>0.77 (0.64-0.92)</td>
<td>0.77 (0.64-0.92)</td>
</tr>
<tr>
<td>Sertraline</td>
<td>94712</td>
<td>514</td>
<td>227451</td>
<td>0.90 (0.79-1.02)</td>
<td>0.91 (0.80-1.03)</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>82879</td>
<td>464</td>
<td>187247</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
</tr>
</tbody>
</table>

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<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Citalopram</td>
<td>30152</td>
<td>46</td>
<td>62420</td>
<td>1.22 (0.84-1.78)</td>
<td>1.27 (0.87-1.85)</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>38634</td>
<td>40</td>
<td>78919</td>
<td>0.85 (0.57-1.25)</td>
<td>0.91 (0.61-1.35)</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>1113</td>
<td>&lt;10</td>
<td>2783</td>
<td>0.61 (0.09-4.40)</td>
<td>0.66 (0.09-4.75)</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>8639</td>
<td>11</td>
<td>19796</td>
<td>0.93 (0.49-1.76)</td>
<td>1.17 (0.62-2.23)</td>
</tr>
<tr>
<td>Sertraline</td>
<td>64537</td>
<td>90</td>
<td>136058</td>
<td>1.11 (0.81-1.52)</td>
<td>1.22 (0.88-1.69)</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>52774</td>
<td>68</td>
<td>113885</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
</tr>
</tbody>
</table>

Conclusions
This cohort study found that treatment with SSRIs during childhood and adolescence may be associated with a small increased risk of T2D, particularly among publicly insured patients. The magnitude of association was more modest than previously reported, and the absolute risk was small, providing evidence that this safety concern is not as substantial as initially reported. This potential risk, which is much lower in magnitude than the other known risk factors for T2D, should be weighed against the known benefits and risks of SSRI treatment to help inform treatment decision making in the pediatric population.

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