Published in final edited form as:

Pharmacoepidemiol Drug Saf. 2015 June ; 24(6): 583–591. doi:10.1002/pds.3768.

Atypical antipsychotic initiation and the risk of type II diabetes in children and adolescents

Minji Sohn^{1,2,3}, Jeffery Talbert^{1,2}, Karen Blumenschein^{1,2}, and Daniela Claudia Moga^{1,2,4,*}

¹College of Pharmacy, Department of Pharmacy Practice and Science, University of Kentucky, Lexington, KY, USA

²Institute for Pharmaceutical Outcomes and Policy, University of Kentucky, Lexington, KY, USA

³Department of Pharmaceutical Sciences, College of Pharmacy, Ferris State University, Big Rapids, MI, USA

⁴Department of Epidemiology, College of Public Health, University of Kentucky, Lexington, KY, USA

Abstract

Purpose—To estimate the risk of type II diabetes (T2DM) in children and adolescents initiating atypical antipsychotic (AAP) therapy.

Methods—We conducted a retrospective cohort study using a new user design approach. Medical and pharmacy claims data between 1 January 2007 and 31 December 2009 for dependents ages 4 to 18 from an employed, commercially insured population from across the USA were included. AAP exposure was defined in the presence of a pharmacy claim preceded by at least six months of AAP-free history. We used propensity score (PS) methodology to identify and match incident AAP users and non-users. New-onset T2DM, was defined based on medical and pharmacy claims. Follow-up was extended until the date of new-onset T2DM or the end of the study period. The risk of T2DM was evaluated in an intent to treat fashion using the Kaplan–Meier estimator and Cox proportional hazard regression that provided hazard ratio (HR) and associated 95% confidence interval (CI).

Results—Our study population included 6236 new AAP users and 22 080 non-users. In this PS-matched sample, the estimated risk of T2DM was twice as high in AAP users as non-users (HR 2.18, 95% CI 1.45–3.29). Noticeable risk differences between AAP-treated and control groups materialized within four months of AAP initiation and became constant after six months until the end of the follow-up.

*Correspondence to: D. C. Moga, Department of Pharmacy Practice and Science, College of Pharmacy University of Kentucky, 789 South Limestone, Room 241, Lexington, KY 40536-0596, USA. daniela.moga@uky.edu.

CONFLICT OF INTEREST

The authors have declared that there is no conflict of interest.

ETHICS STATEMENT

Data use was approved by the University of Kentucky Institutional Review Board, which oversees the ethical conduct of research at this institution. Given that all data were previously collected for purposes other than research and were de-identified, informed consent was not required.

FINANCIAL DISCLOSURE

The authors have no financial relationships relevant to this article to disclose.

Conclusions—Children and adolescents who were prescribed an AAP medication had a two times higher risk of developing T2DM; our study raises questions about continued AAP use in children and adolescents.

Keywords

atypical antipsychotics; type II diabetes; children; risk; pharmacoepidemiology

INTRODUCTION

Despite the safety concerns (i.e., metabolic syndrome, cardiovascular events, or death)^{1–3} raised by postmarketing studies, atypical antipsychotic (AAP) use increased not only for indications approved by the U.S. Food and Drug Administration but also for other conditions.⁴ Moreover, in children and adolescents in the U.S., AAPs are among the most increasingly used classes of prescription drugs.^{5,6} In a study using data from three Medicaid programs and one private managed care organization in the U.S., the total AAP use for children and adolescents increased 1.5-fold to 3-fold between 1996 and 2001.⁶ Also, medical office visits including antipsychotic medications for youth patients increased 5-fold between 1993 and 2002.⁷ This increase is concerning on the risk of developing chronic conditions suggested by previous studies, such as obesity^{8–13} or type II diabetes (T2DM) in children and adolescents taking these drugs.^{14–16} While several postmarketing studies examined weight gain and obesity and provided solid support for the risk, the evidence regarding the risk of T2DM is still limited in younger populations. Although there are plausible mechanisms to support the hypothesized risk for T2DM,^{17,18} current literature evaluating the relationship between AAP use and diabetes in children and adolescents failed to discriminate between type I diabetes (T1DM) and T2DM¹⁴, thus resulting in an underestimation of the true effect.¹⁹ A recent study evaluated this specific AAP–T2DM relationship, but the study population was restricted to a single-state Medicaid population.¹⁵ Findings from a single-state Medicaid program may not be generalizable to a broader population.²⁰ Therefore, the purpose of this paper was to estimate the risk of developing T2DM for children and adolescents who are prescribed an AAP, using nationally representative health care claims data in the U.S.

METHODS

Data source and study population

Through a new user design approach,²¹ we assembled a retrospective cohort of children and adolescents using enrollment files, medical and pharmacy claims data from a health insurance plan in the U.S. These data contain information for a de-identified, nationally representative sample of an employed, commercially insured population including dependents. Members between the ages of 4 to 18 at index date (described in the succeeding text), who were continuously enrolled between January 1, 2007 and December 31, 2009, were considered for this study. Data use was approved by the University of Kentucky Institutional Review Board, which oversees the ethical conduct of research at this institution. Given that all data were previously collected for purposes other than research and were de-identified, informed consent was not required.

Exposure

Our study compared an AAP user group to a similar group of subjects with no exposure to AAPs (non-users). Subjects were considered to be exposed to an AAP if they had at least one prescription for any of the available AAPs, which include aripiprazole, olanzapine, paliperidone, quetiapine, risperidone, and ziprasidone. AAP users were classified as incident or new users (AAP users, hereafter) and included in the analysis if they met all of the following eligibility criteria: (1) initial dispensing date of an AAP (defined as the index date) was preceded by a minimum of six months of continuous enrollment in the health plan (i.e., pre-index period), (2) did not have prescriptions for typical antipsychotics during the six months of the pre-index period, (3) had no history of T1DM or T2DM during the six month pre-index period (refer in the succeeding text for details on defining diabetes), and (4) had evidence of resource utilization in the database (i.e., at least one claim of any type during the pre-index period). This requirement was made to exclude individuals with multiple health insurers (i.e., a child whose parents hold multiple health insurance plans) and made claims primarily to a plan other than the one used in this paper, thus preventing misclassification because of out-of-insurance service utilization. For the comparison group of non-users, index dates were assigned to mirror the distribution of time between January 1, 2007 and AAP initiation date in the AAP treated group. Assigning an index date for non-users was necessary to allow for implementation of eligibility criteria and for evaluation of baseline characteristics used for matching (refer in the succeeding text for detailed description of the matching process) in a similar manner for the two study groups (i.e., AAP users and non-users). Specifically, after identifying AAP users, we evaluated the distribution of time between January 1, 2007 and first AAP prescription date. The percent distribution by the month of index date in AAP users was then mirrored in the non-user group. As a final step, we compared the distribution of time to index date in the two groups to assure that no statistically significant differences were noted. A flow diagram describing the identification process for the groups included in the analyses is depicted in Figure 1.

The follow-up time for each subject started on the index date and was extended until the earliest of (1) T2DM onset or (2) the end of the study period. This approach was intended in order to emulate an intention to treat analysis, similar to randomized controlled trials.

Outcome

The outcome of interest in our study was new-onset T2DM and was identified using medical and pharmacy claims and following the algorithm developed by Bobo *et al.* (2012).²² We used the International Classification of Diseases, 9th Clinical Modification diagnosis codes (250, 250.0, 250.1, 250.2, 250.3, and 250.9) and the National Drug Codes for antidiabetic medications (insulin, insulin adjuncts, alpha-glucosidase inhibitor, amylin analogs, meglitinides, sulfonylureas, and thiazolidinediones) to identify diabetes-related medical/pharmacy care encounters. In order to classify a patient as having T2DM, we required (1) a hospital discharge with a primary diagnosis code for T2DM as described previously or (2) a combination of at least two diabetes-related medical and/or pharmacy claims. When only prescription claims indicated diabetes, T2DM was further separated from T1DM by excluding those with an insulin prescription with no prescriptions for oral antidiabetic medication. The date of onset for T2DM was determined as the date of the first medical/

pharmacy care encounter related to T2DM. However, if a diabetes-related laboratory procedure (i.e., hemoglobin A1c, islet cell antibody test, insulin radioimmunoassay, or metabolic panel) was performed within 30 days before the first diabetes-related medical/pharmacy care encounter, the date of the procedure was considered as the date of T2DM onset.

Covariates

To control for potential selection bias and confounding, non-users were matched to AAP users using the propensity score (PS) matching method.²³ The PS for each participant was estimated through logistic regression as the probability of starting AAP treatment during the study period, based on baseline characteristics. We used causal diagrams^{24,25} to select important covariates for inclusion in the logistic regression model; specifically, the following covariates were included: age, sex, race, geographic region, household income, the year of index date, health care utilization intensity, and medical history during the pre-index period. Health care utilization intensity was measured by four variables: the number of hospitalizations, the number of emergency room (ER) visits, the number of outpatient services, and the number of filled prescriptions with different generic names. Medical history was measured through other medications used (i. e., benzodiazepines and antidepressants), as well as comorbidities (pregnancy, obesity, and cardiovascular diseases).

Analysis

Baseline characteristics of AAP users and non-users were compared and tested before and after PS matching using standardized differences.^{26,27} Using PS, up to four non-users were matched to every AAP new user. The propensity to receive an AAP was estimated through unconditional logistic regression, and the greedy matching algorithm²⁸ with calipers equal to 0.2 of the standard deviation of the logit of the PS was used for matching.²⁹

The rates of developing T2DM in the AAP-treated group and control group were estimated and compared using the Kaplan–Meier (KM) estimator. Cox proportional hazard regression was performed to estimate the risk of T2DM associated with AAP initiation. We concluded that the proportional hazards assumption was not violated because no evidence of interaction between AAP use and time was observed. (HR 0.75, $P = 0.223$). To evaluate the robustness of the finding about the risk of T2DM, sensitivity analyses were conducted by PS distribution trimming, in which those with extreme scores (1% and 5 of each tail) were excluded from the estimation.

All analyses were two-tailed with a type I error level set at 0.05. All statistical analyses were conducted using SAS version 9.3 (SAS Institute Inc., Cary, NC).

RESULTS

Baseline characteristics of non-matched samples

A total of 403 345 children and adolescents met our inclusion criteria. Among those, 6510 individuals were AAP new users. A majority of AAP users received risperidone ($n = 2608$, 40.1%), aripiprazole ($n = 2044$, 31.4%), or quetiapine ($n = 1439$, 22.1%). A relatively small

proportion of AAP users received olanzapine ($n = 239$, 3.7%), ziprasidone ($n = 168$, 2.6%), or paliperidone ($n = 50$, 0.8%). There were 38 (0.6%) individuals who received two AAP agents on the index date. Other baseline characteristics before matching are summarized in Table 1. In the non-matched sample, AAP users were more likely to be adolescents (ages 12–18) and male individuals than non-users. On average, the annual household income was lower for AAP users. Also, the AAP users showed a higher level of health care utilization during the six month pre-index period, as measured by the number of outpatient service visits, hospitalizations, ER visits, and filled prescriptions. The baseline comorbidities and drug use profiles also showed large differences between the two groups in several respects: AAP users had higher prevalence rates of obesity and cardiovascular disease. Also, they showed a higher rate of use for benzodiazepines and antidepressants.

Calculation of PS

The logistic regression model to evaluate AAP utilization is described in Table 2. The results indicate that older patients were more likely to receive an AAP. Female patients were less likely to receive an AAP compared with male patients. Also, western regions of the U.S. were more likely to use an AAP compared with northeastern regions. Annual household income was significantly associated with AAP use: the propensity to receive an AAP decreased as the level of household income increased (Table 2). The higher level of health care utilization measured in the number of outpatient service visits, hospitalizations, and prescriptions significantly increased the propensity to receive an AAP.

Baseline characteristics of PS-matched sample

The final study sample after PS matching consisted of 6236 incident AAP users and 22 080 non-users. The characteristics of matched samples are summarized in Table 1 (right). In this matched sample, AAP new users and matched non-users were balanced on all of the characteristics included in the PS model (standardized differences were smaller than 5%). Figure 2 shows the kernel density estimates of the PS distribution between the two groups. The upper panel depicts the distribution for the non-matched sample, while the lower panel represents the matched sample, showing the similarity between the two groups after PS matching.

The risk of T2DM

The follow-up schedule was very similar between AAP user and non-user groups. In each group, the mean follow-up time was 1.3 (± 0.7) years. The total follow-up time was 8161 person-years in the AAP user group, and 28 792 person-years in the non-user group. During the follow-up, a total of 64 subjects developed T2DM, 27 in the AAP user group (33.1 cases per 10 000 person-years) and 37 in the non-user group (12.9 cases per 10 000 person-years).

The rate of developing T2DM in the matched sample is represented using the KM estimator (Figure 3). The risk difference between two groups appeared at approximately four months after the index date, and it increased rapidly between four months and six months after the index date. After six months, the risk difference was almost constant until the end of the follow-up. The estimated risk of T2DM was twice higher in AAP users than non-users in the PS matched sample (HR 2.18, 95% confidence interval (CI): 1.45, 3.29). This finding was

robust in sensitivity analyses in which 1 and 5% of each tail of the PS distribution were excluded from the analysis (HR 2.46, 95% CI: 1.56, 3.88 ; HR 2.62, 95% CI: 1.38, 4.96, respectively).

DISCUSSION

The purpose of this study was to examine the association between AAP initiation and T2DM in children and adolescents. We found that initiation of AAP increased the risk of developing T2DM about two-fold for those between the ages of 4 and 18. While T2DM is known to develop slowly over months or years, the fact that noticeable risk differences between AAP-treated and comparison groups emerged between four and six months are striking. This result is in good agreement with a recent study published by Bobo and collaborators.¹⁵ They conducted a retrospective cohort study for children and youth, using Tennessee Medicaid health care claims data and reported a three-fold higher risk of T2DM imposed on antipsychotic medication users (both typical and atypical), compared with PS-matched users of other psychotropic drugs. Our observation on the probability of developing T2DM during the course of the follow-up assessment (KM curve) is very similar to the result reported by Bobo and colleagues (Figure 2). For example, at the 20 month (600 days) follow-up, the probability of T2DM is approximately 0.004 for the treatment group and 0.002 for the control group in both studies. The fact that the point estimate of the hazard ratio reported by Bobo *et al.* is different from what we found is likely because of differences in study design, specifically (1) different follow-up periods (longer for Bobo *et al.*) and/or (2) study population (Tennessee Medicaid versus U.S. commercially insured). Another study previously conducted by Andrade *et al.* concerned the risk of diabetes associated with antipsychotic medication use in children and adolescents (ages of 5 to 18).¹⁴ They used a large diverse cohort from Health Maintenance Organization databases and did not find a significant association between AAPs and diabetes in PS-matched samples. One of the major differences between our study design and theirs was the inclusion of T1DM in study outcomes. However, a majority of diabetes patients in children are likely to be type I¹⁹, and the concerns about AAP adverse side effects are often associated with type II.^{17,18} Therefore, including T1DM as an outcome could have attenuated the risk of AAPs in their study.

In our PS-matched cohort, a majority of individuals were adolescents with ages between 12 and 18 (61%), male (63%), and white (78%). Approximately 47% resided in the south region of the U.S. and more than half of the sample belonged to households with an annual income greater than \$60 000. During the six month pre-index period, 86% had not been hospitalized and 98% had not visited ER. Also, 5% used benzodiazepines and 31% used antidepressants during the period. These factors could have affected results and need to be taken into account when implementing the findings of this paper.

It should be noted that the individuals who were identified as having new-onset T2DM are subject to a potential misclassification. The algorithm we adopted for this study was developed from a Tennessee Medicaid program, and it is possible that the algorithm did not effectively identify true T2DM cases in our database. If diabetes management or diabetes related claim filing processes vary largely by the payer source or geographical regions, it

may affect our conclusion about the impact of AAPs on T2DM. Another limitation of our study is a relatively short follow-up. The longest possible follow-up period in this paper was 2.5 years, and this does not adequately capture the longer-term impact of AAPs on T2DM. Also, the small number of new-onset T2DM cases limited our ability to assess the differential impact of AAPs on different strata such as patient demographics and socioeconomic factors. In addition, our limited sample size and the small number of events during the relatively short follow-up available in the data did not allow for separate analyses for the different AAPs.

Having non-users as the comparison group might have overestimated the risk of T2DM for AAP users because AAP users could be more frequently monitored for T2DM than non-users. However, to minimize the potential differences in monitoring between the two cohorts, we only chose non-users who were similar to AAP users in baseline characteristics. Moreover, the fact that our study reports similar findings to a previous study, using an active comparator¹⁵ supports the reliability of our study design.

Although it was not the primary interest for our paper, our logistic regression model revealed important factors associated with AAP use (Table 2). First, female patients were less likely to receive an AAP compared with male patients (odds ratio (OR) 0.54, 95% CI: 0.51, 0.57). This is consistent with the national trend, in which female patients are outnumbered by male patients in children and adolescent psychiatric services.³⁰ Second, the propensity of a patient to receive an AAP decreased gradually as the household income increased. In other words, if a patient was from a high-income family, the patient was less likely to use an AAP. This finding has an important implication about the role of one's socioeconomic status that affects exposure to an AAP.

Our study adds strong evidence to the existing literature and overcomes some of the limitations of previous research. First, our report critically examined patients who possessed a commercial health care plan within the U.S., who were either commercially insured or enrolled in a Medicaid managed care plan. This consideration cannot be understated, because commercial insurance and Medicaid are the two largest payers of mental health services in the USA.³¹ Therefore, the findings of this paper are generalizable to a larger population. Second, we sought to avoid selection bias by matching subjects based on their propensity to receive an AAP. Before matching, there was a considerable difference observed in baseline characteristics between AAP users and non-users. Atypical antipsychotic users were more likely to be obese and receive intense health care services such as hospitalizations and ER visits. (Table 1, left) This suggests the presence of potential selection bias in the non-matched cohort, in which AAP users had inherently higher risk of developing a chronic illness including T2DM than non-users before they were exposed to an AAP. In our PS matched cohort, baseline characteristics were similar between AAP users and non-users.

We found that children and adolescents who use an AAP medication had a two times higher risk of developing T2DM within six months of initiating medication when compared with PS-matched non-users from nationally representative health care claims in the U.S. Given the lack of strong evidence regarding long-term effectiveness on which to base clinical

practice recommendations,^{32,33} our results suggest that greater caution should be taken when considering AAP treatment in children and adolescents. Considering that T2DM is a chronic condition that may persist for the rest of a person's life, it is critical to justify AAP treatment with accurate diagnosis and clinical evidence and to individualize the decision based on each patient's risk-benefit profile.

Acknowledgments

FUNDING SOURCE

The project described was supported by the National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health, through grant 8UL1TR000117-02. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. Dr. Moga is supported by grant number K12 DA035150 from the National Institutes of Health, Office of Women's Health Research and the National Institute on Drug Abuse.

REFERENCES

1. Lieberman JA, Stroup TS, McEvoy JP, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *The New England journal of medicine*. 2005; 353(12):1209–1223. [PubMed: 16172203]
2. Bobes J, Arango C, Aranda P, et al. Cardiovascular and metabolic risk in outpatients with schizophrenia treated with antipsychotics: results of the CLAMORS Study. *Schizophrenia research*. 2007; 90(1-3):162–173. [PubMed: 17123783]
3. Friedman JH. Atypical antipsychotics in the elderly with Parkinson disease and the 'black box' warning. *Neurology*. 2006; 67(4):564–566. [PubMed: 16924004]
4. Alexander GC, Gallagher SA, Mascola A, Moloney RM, Stafford RS. Increasing off-label use of antipsychotic medications in the United States, 1995–2008. *Pharmacoepidemiology and drug safety*. 2011; 20(2):177–184. [PubMed: 21254289]
5. Zito JM, Safer DJ, DosReis S, et al. Psychotropic practice patterns for youth: a 10-year perspective. *Archives of pediatrics & adolescent medicine*. 2003; 157(1):17–25. [PubMed: 12517190]
6. Patel NC, Crismon ML, Hoagwood K, et al. Trends in the use of typical and atypical antipsychotics in children and adolescents. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2005; 44(6):548–556. [PubMed: 15908837]
7. Olfson M, Blanco C, Liu L, Moreno C, Laje G. National trends in the outpatient treatment of children and adolescents with antipsychotic drugs. *Archives of general psychiatry*. 2006; 63(6):679–685. [PubMed: 16754841]
8. Maayan L, Correll CU. Weight gain and metabolic risks associated with antipsychotic medications in children and adolescents. *Journal of child and adolescent psychopharmacology*. 2011; 21(6):517–535. [PubMed: 22166172]
9. Kelly DL, Conley RR, Love RC, Horn DS, Ushchak CM. Weight gain in adolescents treated with risperidone and conventional antipsychotics over six months. *Journal of child and adolescent psychopharmacology*. 1998; 8(3):151–159. [PubMed: 9853689]
10. Martin A, Landau J, Leebens P, et al. Risperidone-associated weight gain in children and adolescents: a retrospective chart review. *Journal of child and adolescent psychopharmacology*. 2000; 10(4):259–268. [PubMed: 11191686]
11. Correll CU, Manu P, Olshanskiy V, Napolitano B, Kane JM, Malhotra AK. Cardiometabolic risk of second-generation antipsychotic medications during first-time use in children and adolescents. *JAMA : the journal of the American Medical Association*. 2009; 302(16):1765–1773. [PubMed: 19861668]
12. de Hoogd S, Overbeek WA, Heerdink ER, Correll CU, de Graeff ER, Staal WG. Differences in body mass index z-scores and weight status in a Dutch pediatric psychiatric population with and without use of second-generation antipsychotics. *Journal of child and adolescent psychopharmacology*. 2012; 22(2):166–173. [PubMed: 22506734]

13. Moreno C, Merchan-Naranjo J, Alvarez M, et al. Metabolic effects of second-generation antipsychotics in bipolar youth: comparison with other psychotic and nonpsychotic diagnoses. *Bipolar Disord.* 2010; 12(2):172–184. [PubMed: 20402710]
14. Andrade SE, Lo JC, Roblin D, et al. Antipsychotic medication use among children and risk of diabetes mellitus. *Pediatrics.* 2011; 128(6):1135–1141. [PubMed: 22106077]
15. Bobo WV, Cooper WO, Stein CM, et al. Antipsychotics and the risk of type 2 diabetes mellitus in children and youth. *JAMA psychiatry.* 2013; 70(10):1067–1075. [PubMed: 23965896]
16. McIntyre RS, Jerrell JM. Metabolic and cardiovascular adverse events associated with antipsychotic treatment in children and adolescents. *Archives of pediatrics & adolescent medicine.* 2008; 162(10):929–935. [PubMed: 18838645]
17. Smith M, Hopkins D, Peveler RC, Holt RI, Woodward M, Ismail K. First- v. second-generation antipsychotics and risk for diabetes in schizophrenia: systematic review and meta-analysis. *The British journal of psychiatry : the journal of mental science.* 2008; 192(6):406–411. [PubMed: 18515889]
18. Lean ME, Pajonk FG. Patients on atypical antipsychotic drugs: another high-risk group for type 2 diabetes. *Diabetes care.* 2003; 26(5):1597–1605. [PubMed: 12716824]
19. Vanderloo SE, Johnson JA, Reimer K, et al. Validation of classification algorithms for childhood diabetes identified from administrative data. *Pediatric diabetes.* 2012; 13(3):229–234. [PubMed: 21771232]
20. Shatin D, Levin R, Ireys HT, Haller V. Health care utilization by children with chronic illnesses: a comparison of medicaid and employer-insured managed care. *Pediatrics.* 1998; 102(4):E44. [PubMed: 9755281]
21. Ray WA. Evaluating medication effects outside of clinical trials: new-user designs. *American journal of epidemiology.* 2003; 158(9):915–920. [PubMed: 14585769]
22. Bobo WV, Cooper WO, Stein CM, et al. Positive predictive value of a case definition for diabetes mellitus using automated administrative health data in children and youth exposed to antipsychotic drugs or control medications: a Tennessee Medicaid study. *BMC medical research methodology.* 2012; 12:128. [PubMed: 22920280]
23. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika.* 1983; 70(1):41–55.
24. Textor J, Hardt J, Knuppel S. DAGitty: a graphical tool for analyzing causal diagrams. *Epidemiology.* 2011; 22(5):745. [PubMed: 21811114]
25. Hernan MA, Hernandez-Diaz S, Robins JM. A structural approach to selection bias. *Epidemiology.* 2004; 15(5):615–625. [PubMed: 15308962]
26. Flury BK, Riedwyl H. Standard distance in univariate and multivariate analysis. *Am Stat.* 1986; 40(3):249–251.
27. Austin PC. Using the standardized difference to compare the prevalence of a binary variable between two groups in observational research. *Commun Stat-Simul C.* 2009; 38(6):1228–1234.
28. Bergstralh EJ, Kosanke JL, Jacobsen SJ. Software for optimal matching in observational studies. *Epidemiology.* 1996; 7(3):331–332. [PubMed: 8728456]
29. Austin PC. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. *Pharmaceutical statistics.* 2011; 10(2):150–161. [PubMed: 20925139]
30. Walrath CM, Petras H, Mandell DS, Stephens RL, Holden EW, Leaf PJ. Gender differences in patterns of risk factors among children receiving mental health services: latent class analyses. *The journal of behavioral health services & research.* 2004; 31(3):297–311. [PubMed: 15263868]
31. SAMHSA. National expenditures for mental health services and substance abuse treatment, 1986-2005. 2010. DHHS Publication No. (SMA) 10-4612
32. Christian RB, Gaynes BN, Saavedra LM, et al. Use of antipsychotic medications in pediatric and young adult populations: future research needs. *Journal of psychiatric practice.* 2015; 21(1):26–36. [PubMed: 25603449]
33. Seida, JC.; Schouten, JR.; Mousavi, SS., et al. First- and Second-Generation Anti-psychotics for Children and Young Adults. Rockville (MD): 2012.

KEY POINTS

- Previous studies suggested an association between atypical antipsychotics and diabetes in general, but the evidence of a causal relationship between these drugs and type II diabetes is still limited, especially in children and adolescents.
- Our investigation in a large sample of the U.S. 4-year to 18-year-old population brings evidence for a two times higher risk of developing of type II diabetes in atypical antipsychotic users as compared with non-users.

Figure 1.
Sample selection flowchart

Figure 2.
Propensity score distribution before (top) and after (bottom) matching

Figure 3.
KM curve estimating the probability of T2DM in the PS matched sample

Table 1

Baseline characteristics

	Before matching						After matching					
	AAP users (n = 6510)			Non-users (n = 396 835)			AAP users (n = 6236)			Non-users (n = 22 080)		
	n	%		n	%	Std. Diff. [†]	n	%		n	%	Std. Diff. [†]
Baseline characteristics												
Age												
4–5	246	3.8		57 793	14.6	0.380	245	3.9		1056	4.8	0.018
6–11	2023	31.1		164 612	41.5	0.218	1994	32.0		7721	35.0	0.024
12–18	4241	65.2		174 430	44.0	0.436	3 997	64.1		13 303	60.3	0.031
Sex												
Male	3978	61.1		203 505	51.3	0.199	3802	61.0		13 901	63.0	0.030
Female	2532	38.9		193 330	48.7	0.199	2434	39.0		8179	37.0	0.030
Race												
White	5126	78.7		297 885	75.1	0.087	4910	78.7		17 274	78.2	0.008
Black	288	4.4		15 199	3.8	0.030	275	4.4		976	4.4	0.001
Hispanic	431	6.6		34 211	8.6	0.075	414	6.6		1494	6.8	0.001
Others	617	9.5		46 812	11.8	0.075	592	9.5		2087	9.5	0.003
Region of residence												
Northeast	712	10.9		48 113	12.1	0.037	690	11.1		2357	10.7	0.015
Midwest	1731	26.6		102 996	26.0	0.014	1647	26.4		5826	26.4	0.007
South	3074	47.2		190 671	48.1	0.017	2944	47.2		10 430	47.2	0.006
West	993	15.3		54 942	13.9	0.040	955	15.3		3464	15.7	0.013
Annual household income												
\$29 999	207	3.2		10 152	2.6	0.037	193	3.1		764	3.5	0.020
\$30 000–39 999	364	5.6		17 593	4.4	0.053	348	5.6		1350	6.1	0.017
\$40 000–49 999	585	9.0		32 271	8.1	0.031	558	9.0		1974	8.9	0.004
\$50 000–59 999	596	9.2		35 877	9.0	0.004	570	9.1		2102	9.5	0.010
\$60 000–74 999	790	12.1		51 644	13.0	0.027	757	12.1		2702	12.2	0.001
\$75 000–99 999	1,170	18.0		81 702	20.6	0.066	1133	18.2		3880	17.6	0.013
\$100 000	1,563	24.0		115 304	29.1	0.114	1520	24.4		5171	23.4	0.024
Number of outpatient												

Baseline characteristics	Before matching				After matching			
	AAP users (n = 6510)		Non-users (n = 396 835)		AAP users (n = 6236)		Non-users (n = 22 080)	
	n	%	n	%	n	%	n	%
service visits [*]								
0–5	2357	36.2	330 942	83.4	2353	37.7	8858	40.1
6+	4153	63.8	65 893	16.6	3883	62.3	13 222	59.9
Number of drugs prescribed (different generic name drugs) [*]								
0–3	3045	46.8	326 225	82.2	3012	48.3	11 513	52.1
4+	3465	53.2	70 610	17.8	3224	51.7	10 567	47.9
Number of hospitalizations [*]								
0	5214	80.1	392 254	98.9	5202	83.4	19 315	87.5
1–3	1273	19.6	4500	1.1	1012	16.2	2721	12.3
4+	23	0.4	81	<0.1	22	0.4	44	0.2
Number of ER visits [*]								
0	6413	98.5	393 944	99.3	6145	98.5	21 811	98.8
1+	97	1.5	2891	0.7	91	1.5	269	1.2
Baseline comorbidities and drug use								
Obesity	157	2.4	4086	1.0	150	2.4	458	2.1
Cardiovascular disease	259	4.0	4504	1.1	240	3.9	714	3.2
Pregnancy	9	0.1	336	0.1	9	0.1	30	0.1
Benzodiazepine use	460	7.1	2764	0.7	413	6.6	976	4.4
Antidepressant use	2648	40.7	9439	2.4	2374	38.1	6409	29.0

^{*} Variables categorized based on frequency distribution;

[†] no statistical difference if std. diff. < 10% (0.10).

Table 2

Propensity score model of receiving an AAP medication

Covariate	OR*	95% CI [†]
Age		
4–5	Reference	
6–11	2.68	2.34, 3.01
12–18	3.26	0.85, 3.73
Sex		
Male	Reference	
Female	0.54	0.51, 0.57
Race		
White	Reference	
Black	1.25	1.10, 1.43
Hispanic	0.86	0.77, 0.95
Others	0.88	0.80, 0.97
Region of residence		
Northeast	Reference	
Midwest	0.99	0.91, 1.10
West	1.07	1.23, 1.52
South	1.07	0.98, 1.17
Annual household income		
\$29 999	Reference	
\$30 000–39 999	1.01	0.89, 1.15
\$40 000–49 999	0.80	0.72, 0.89
\$50 000–59 999	0.74	0.66, 0.82
\$60 000–74 999	0.63	0.57, 0.69
\$75 000–99 999	0.58	0.53, 0.63
\$100 000	0.48	0.44, 0.52
Number of outpatient visits		
0–5	Reference	
6+	3.84	3.61, 4.08
Number of drugs prescribed (different generic name drugs)		
0–3	Reference	
4+	2.04	1.93, 2.17
Number of hospitalizations		
0	Reference	
1–3	5.94	5.45, 6.47
4+	3.10	1.78, 5.40
Number of ER visits		
0	Reference	
1+	0.77	0.60, 0.98

Covariate	OR*	95% CI [†]
Baseline comorbidities and drug use		
Obesity	1.03	0.85, 1.24
Cardiovascular disease	0.79	0.68, 0.93
Pregnancy	0.31	0.15, 0.645
Benzodiazepine use	1.95	1.71, 2.22
Antidepressant use	12.01	11.28, 12.80

* OR, Odds ratio.

[†] 95% CI, 95% confidence interval.