MINI-SENTINEL ASSESSMENT
METABOLIC EFFECTS OF SECOND GENERATION ANTIPSYCHOTICS IN YOUTH

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Mini-Sentinel is a pilot project sponsored by the U.S. Food and Drug Administration (FDA) to inform and facilitate development of a fully operational active surveillance system, the Sentinel System, for monitoring the safety of FDA-regulated medical products. Mini-Sentinel is one piece of the Sentinel Initiative, a multi-faceted effort by the FDA to develop a national electronic system that will complement existing methods of safety surveillance. Mini-Sentinel Collaborators include Data and Academic Partners that provide access to health care data and ongoing scientific, technical, methodological, and organizational expertise. The Mini-Sentinel Coordinating Center is funded by the FDA through the Department of Health and Human Services (HHS) Contract number HHSF223200910006I.

Mini-Sentinel Assessment
Metabolic Effects Of Second Generation Antipsychotics In Youth

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I. INTRODUCTION

A. BACKGROUND

Over the past several years, the number of children and adolescents treated with antipsychotic medications has markedly increased.[1-3] Using data from the National Ambulatory Medical Care Survey and US Census Bureau data, one recent study estimated that outpatient visits with a prescription for antipsychotic medications per 100 persons between 1993-1998 and 2005-2009 increased from 0.24 to 1.83 for children (0-13 years) and from 0.78 to 3.76 for adolescents (14-20 years).[3] Over the last decade, prescribing of antipsychotic medications in the pediatric population has been almost exclusively limited to the second generation antipsychotics (SGAs).[1]

FDA-approved indications for antipsychotic medications in children and adolescents (based on approval of ≥1 antipsychotic agent) include schizophrenia (13-17 years), irritability/aggression associated with autistic disorder (5-17 years), bipolar mania (10-17 years), and tics and vocal utterances of Tourette's disorder (See AHRQ Publication No. 12-EHC042-EF for a comprehensive listing of FDA-approved indications and age groups for first and second generation antipsychotics).[4] In adults, antipsychotic medications are also approved for bipolar depression and as an adjunctive treatment for major depression. While the increasing use of antipsychotic medications in children and adolescents has coincided with an increase in the diagnosis of bipolar disorder and autism spectrum disorders in this age group,[5-7] a majority of use is off label, most commonly for ADHD and other disruptive disorders.[1, 3, 8]

In adults, SGAs cause weight gain and adverse metabolic effects, such as lipid and glucose abnormalities that differ across individual agents.[9] Children and adolescents may be at even greater risk for these adverse effects than adults, in large part due to the fact that a greater proportion of patients in this age group is SGA naïve.[10, 11] In 2003, the FDA issued warnings regarding increased risk for hyperglycemia and diabetes mellitus for all SGAs and guidelines recommend metabolic screening and monitoring.[12] Limited evidence from observational studies in adults treated with SGAs suggests marked differences in the risk for type 2 diabetes between individual SGAs,[13, 14] though not all studies have reported such differences.[15] In children and adolescents, one recent study reported an increased rate of diabetes among 5-18 year olds exposed to SGAs, but results were inconsistent and strongly depended on the comparison group.[16]

One limitation both clinically and for the epidemiologic study of diabetes risk associated with medication exposure is the inappropriately low diabetes and dyslipidemia monitoring rate in clinical care. Despite availability of multiple national and international monitoring guidelines,[17] monitoring for diabetes has been inadequately low both in adults (glucose: 44%, HbA1C: 25%),[18] and in youth (glucose: 16-32%)[19, 20] exposed to antipsychotic treatment.

To date, comparative data for the risk of type 2 diabetes in children and adolescents treated with SGAs is limited to preliminary results of an FDA/AHRQ funded study that estimated the comparative risk for incident type 2 diabetes for individual SGAs in publicly insured youth aged 6-24 years.[21] This study found no evidence of significant differences in type 2 diabetes risk between individual SGAs but the interpretability of its findings is limited by the potential for residual confounding from channeling of patients who, based on their body mass index, metabolic parameters or family history, were perceived to be at high risk of developing type 2 diabetes to antipsychotic agents considered to have less metabolic impact. Data on changes in body composition and other metabolic parameters after initiation

of SGAs in children and adolescents is similarly limited with the most comprehensive data coming from a prospective single-center study of 205 patients aged 4-19 treated for 12 weeks with aripiprazole, olanzapine, quetiapine, or risperidone.[11]

The overall goal of this Mini-Sentinel project is to replicate and improve upon the FDA/AHRQ funded study to determine whether individual SGAs, when used in children and adolescents, are associated with differential risks of developing type 2 diabetes.

B. PROJECT OVERVIEW

The project includes 3 subprojects:

1. Subproject 1

Comparative Analysis of Type 2 Diabetes Risk among Young Patients Newly Initiated on Second Generation Antipsychotics in the Mini-Sentinel Partner Sites.

Subproject 1 aims to replicate (with opportunity for revisions and adjustments) and update an AHRQ and FDA funded study conducted with Medicaid Analytic Extract (MAX) data by the Rutgers and Vanderbilt CERTs. The MAX study compared the risk of incident type 2 diabetes among new users of individual second generation antipsychotic medications (APMs) using near national MAX data from 2001 to 2005. For Subproject 1, the Mini-Sentinel Distributed Database (MSDD) will be employed to define a Mini-Sentinel (MSN) patient cohort of new initiators of SGAs to "replicate" the MAX analyses. Results of Subproject 1 will inform whether or not the model developed using the MAX-derived cohort performs similarly in the MSN-derived cohort. The patient cohort developed in Subproject 1 will be referred to in this document as the Antipsychotics in Youth (APY) cohort.

2. Subproject 2

A) Exploring the Feasibility of Using BMI and Laboratory Data for Baseline Confounding Adjustment in Selected Mini-Sentinel Partner Sites.

A few MSN Data Partners (DPs) have patient height and weight data available from the Electronic Health Records (EHR) of their members. These data have been incorporated into the MSDD. Several MSN DPs have also incorporated glycosylated hemoglobin (HbA1c) and blood glucose laboratory data into the MSDD. However, as these data elements—extracted from information obtained as part of routine clinical care—are newly incorporated into the MSDD, the completeness and timing of these clinical measurements within a cohort of youth newly initiating antipsychotics have not been determined. The specific aims of Subproject 2A: Exploring the Feasibility of Using BMI and Laboratory Data for Baseline Confounding Adjustment in Selected Mini-Sentinel Partner Sites, are therefore to:

1. Determine the proportion of the patients in the APY cohort with height and weight data available at baseline (i.e., within a narrowly-defined time window indexed to date of antipsychotic initiation),
2. Determine the proportion of patients in the APY cohort with baseline HbA1c and/or blood glucose (jointly referred to as "GLU" in this document) laboratory results available,
3. Characterize and compare the proportion of patients with/without baseline height, weight, HbA1c, and/or blood glucose laboratory results data, and
4. Characterize the availability of these data elements based on cohort characteristics including timeframe, age, gender, and specific AP exposure.

B) Integrating BMI and Laboratory Data into Subproject 1 Analyses to Improve Confounding Adjustments.

Conditional on feasibility (e.g. adequate sample size determination in Subproject 1), adequacy of the BMI and laboratory data (Subproject 2A) and continued support from FDA, Subproject 2B will integrate laboratory and BMI data into the Subproject 1 analyses to improve control of confounding. These analyses will be limited to those Data Partners that can provide access to BMI and/or laboratory results.

3. Subproject 3

Examining Longitudinal Change in BMI and Laboratory Parameters between Young Patients Newly Initiated on Individual Second Generation Antipsychotics.

Conditional on adequate data quality (Aim 2a) and continued support from FDA, Subproject 3 aims to examine longitudinal changes in BMI and metabolic lab parameters between individuals initiated on alternative second generation APMs in the APY cohort.

This report covers subprojects 1 and 2A. A protocol that describes the analysis plan for Subprojects 1 and 2A has been posted on the Mini-Sentinel website.[1]

II. SUBPROJECT 1

A. METHODS

1. Data Source

The project includes all Data Partners contributing data to the Mini-Sentinel Distributed Database (not all Data Partners participate in all subprojects). Each individual Data Partner site contributed data in the Mini-Sentinel Common Data Model format based on each site's data availability and completeness at the time of the study (Appendix 1). The data for this project include claims between January 1, 2000 and January 31, 2013.

[1] http://mini-sentinel.org/assessments/medical_events/details.aspx?ID=203

2. Cohort

The study cohort was comprised of persons 2-24 years of age with new treatment episodes involving second generation antipsychotic medications (aripiprazole, olanzapine, risperidone, quetiapine, ziprasidone, asenapine, iloperidone, lurasidone, paliperidone). Clozapine was not included in the study because it is almost exclusively used as a second line agent.[22] The day of the first SGA dispensing was defined as the index date. New treatment episodes were defined as initiation of a study SGA preceded by ≥180 days of plan enrollment with both medical and prescription drug coverage (allowing enrollment lapses of ≤45 days) during which there were no claims for any antipsychotic agent, including first generation agents (non-depot injections were not included as part of the 180 washout period). A 365 day look-back period was used in sensitivity analysis. Cohort membership further required plan enrollment with both medical and prescription drug coverage for 120 days after the index date (required for the case confirmation window described in the *Outcome* section below).

Persons with <2 medical encounters or any long-term care claims during the 180-day pre-index period or <1 medical encounters during the 90-day pre index period were excluded. Additional exclusions were made for serious somatic illness (see Protocol Appendix A, M1), claims indicating the presence of the study endpoint prior to the index date see Protocol Appendix A, M2, pregnancy, polycystic ovarian syndrome, initiation of >1 antipsychotic medication on the index date, or an index dispensing with 0 days of supply.

3. Outcome

The outcome of interest was a diagnosis of Diabetes Mellitus Type 2 as defined by an algorithm based on diagnostic, prescription, and monitoring claims. The construction and validation of this algorithm has been previously described.[23] The positive predictive value of the algorithm for type 2 diabetes was 74.2%. When cases for which type was unspecified in the adjudication were considered as type 2, the positive predictive value of the algorithm increased to 83.9%. The algorithm has been modified for the present study to accommodate differences in the coding of inpatient visits between the Tennessee Medicaid data (with which the case definition was developed and validated) and the MSCDM. Appendix 2 presents the modified version of the algorithm. A secondary outcome definition (positive predictive value: 75.9%), also presented in Appendix 2, was implemented to avoid under ascertainment of type 2 diabetes cases that resolve quickly without pharmacological treatment.

4. Potential for Confounding Variables

We defined a comprehensive set of demographic, diagnostic, healthcare utilization, and medication use covariates, all assessed during the 180 day pre-index period. Details regarding the definition of these covariates can be obtained from Tables 4-14 in the study protocol. The current report presents select summary variables defined in Table 15 of the study protocol.

5. Follow Up

We determined SGA exposure based on the days supply and the dispensing dates of the index agent. Because the days supply variable may be manually entered by the pharmacist, we implemented two quantity adjustments. If the days supply exceeded the quantity dispensed, days supply was replaced by quantity dispensed. In addition, the days supply variable was capped at a maximum of 120 days. The index study SGA was considered to be discontinued (at the last day of supply) if there was a break in supply of >14 days. Early refills (stockpiling) were not explicitly considered but were implicitly considered by allowing breaks of up to 14 days. Follow up began at the index date (initial dispense date

of the index SGA). The end of follow-up (censoring date) for the base case was defined as the first of the following dates:

1. SGA discontinuation +30 days (30 days were added to reduce potential bias from informative censoring if patients discontinue the SGA because of adverse effects experienced shortly before)
2. Addition of 2nd APM/APM switch
3. Day prior to 25th birthday
4. No medical care encounters (day 365 without at least 2 medical encounters)
5. Pregnancy
6. Polycystic ovarian syndrome
7. Serious somatic illness
8. Type 1 diabetes
9. 120 days prior to end of data set (Data Partner specific)
10. 120 days prior to date of death
11. 120 days prior to loss of eligibility
12. Type 2 diabetes

The following 6 alternate specifications were implemented as sensitivity analyses:

(S1) 30 days follow-up added after index AP discontinuation or 2nd APM/APM switch

(S2) 90 days follow-up added after index SGA discontinuation

(S3) No days added after index AP discontinuation or 2nd APM/APM switch

(S4) 180 day intent to treat (index exposure carried forward until day 180)

(S5) 365 day intent to treat (index exposure carried forward until day 365)

(S6) Base case with secondary type 2 diabetes definition

6. Statistical Analysis

We calculated descriptive statistics regarding overall SGA use and study outcomes stratified by age group, sex, Data Partner, and diagnosis. Utilization rates were calculated per 1,000 person years of eligible follow-up. For comparing rates, we used risperidone as the referent medication because it was the most widely used agent.

Data analysis was performed at each individual Data Partner site using standardized distributed SAS programs developed for the Mini-Sentinel common data model. Site-specific aggregate data from each site was then transferred to the Mini-Sentinel Operations Center (MSOC) for further analyses to create MS-wide estimates. No individual-level data were transferred from any of the Data Partners.

a. Comparison of Baseline Characteristics

We compared the baseline characteristics of new users of individual SGAs with risperidone as the referent agent. Data Partners provided summary counts that were combined to calculate summary MS-wide results. Between-group imbalances were compared using standardized differences, calculated as the difference in means or proportions between two groups divided by the pooled estimate of the standard deviation of the two groups.

b. Calculation of Type 2 Diabetes Incidence Rates

We calculated the incidence rate and 95% confidence intervals of type 2 diabetes per 1,000 person-years of follow up for all SGAs combined. Each Data Partner provided site-specific summary counts of incident cases as well as of person time of follow up which were combined to obtain the MS-wide estimates.

c. Calculation of SGA incidence

The descriptive analyses generated overall and site-specific estimates of new SGA use (calculated as an incidence proportion) for each calendar year with complete data. The APY cohort as specified above supplied counts for the numerator of the incidence proportion. The denominator counts were generated from non-users of antipsychotic medications, specifically of all MSDD enrollees age 2-24 who meet the inclusion/exclusion criteria of the APY cohort with the exception of those directly relating to SGA initiation (Protocol Table 2; except criteria 3 and 7f). The index date for the denominator was July 1 of each calendar year with available data. The numerator for each calendar year was number of individuals in the APY cohort with an index date during that year. The denominator for each calendar year was the number of MSDD enrollees who on July 1 of that year meet all eligibility criteria (Protocol Table 2; except criteria 3 and 7f). Stratified analyses were be performed for age and sex (numerator and denominator were stratified based on sex and the age at the index date), as well as by individual SGA (see Tables 1-4 below).

B. RESULTS

We identified 232,631 persons between the ages of 2 and 24 who had a prescription claim for a SGA preceded by ≥180 days of continuous enrollment with pharmacy and medical benefits in one of the 17 Mini-Sentinel Data Partners between January 1, 2000 and January 31, 2013. Of these, 118,247 persons (50.8%) initiated a new SGA treatment episode and met all study inclusion and exclusion criteria (Figure 1). Individual Data Partners contributed between 578 and 39,886 persons to the study cohort.

1. Baseline Patient Characteristics

The mean age of the cohort was 15.5 years with approximately three quarters being 13 years or older. Forty four percent of the cohort were female. Information on race/ethnicity was missing for the majority of the cohort. The most common psychiatric diagnosis groups during the baseline period were depression and other mood disorders (54.5%), ADHD and disruptive behavior disorders (39.3%), anxiety disorders (34.7%), and bipolar disorder (22.0%). Use of psychotropic medications was common with 55.8% of cohort members with claims for antidepressants, 34.8% with claims for ADHD medications, 21.1% with claims for mood stabilizers and 6.7% with claims for anxiolytics.

2. Baseline Patient Characteristics by SGA

The most commonly initiated SGA was risperidone (33.6%), followed by aripiprazole (28.3%), quetiapine (26.8%), olanzapine (8.2%), and ziprasidone (2.5%). The remaining four agents (asenapine, iloperidone, lurasidone, and paliperidone) together made up 0.6% of the study population. We observed marked differences in demographic and clinical characteristics between youth initiating individual SGAs (Tables 1-3). Youth initiating risperidone were more likely to be male and younger. Almost half of risperidone initiators were under the age of 13, with only 11% (olanzapine, quetiapine) and 23% (aripiprazole) in this age group among initiators of other agents. More than half of initiators of olanzapine and quetiapine were 18 years and older, compared to 21% of risperidone initiators. More than half of the initiators of quetiapine (77%) and risperidone (52%) were started on a comparably high dose (>75mg CPZ), while the majority of youth started on olanzapine (71%) and aripiprazole (60%) were started on a comparably low dose (≤75 mg CPZ).

Substantial differences between initiators of different SGAs also existed in baseline psychiatric diagnoses. Risperidone was most commonly used in patients diagnosed with ADHD and disruptive behavior disorders (51%), depression (43%), and pervasive development disorders (15%) and less frequently used in youth diagnosed with schizophrenia (11%), bipolar disorder (15%), and substance use disorders (10%). Olanzapine, in contrast was used more frequently in the youth diagnosed with the latter conditions (23% of use in youth with schizophrenia, 33% of use in youth with bipolar disorder, and 25% of use in youth with substance use disorders) and less commonly used in youth diagnosed with ADHD or disruptive behavior disorders (27%). Quetiapine was most frequently used in youth diagnosed with depression (62%) or anxiety disorders (42%) and aripiprazole in youth with depression (60%) or ADHD or disruptive behavior disorders (39%).

Treatment with other psychiatric medication classes during the baseline period was common and markedly different between individual SGAs. Close to or exceeding 60% of youth initiating aripiprazole, quetiapine or olanzapine had claims for an antidepressant with a somewhat lower rate among risperidone initiators (45%). Risperidone users were the most likely to receive treatment with ADHD medications (45%) with lower rates ranging from 21% to 35% for the other commonly used SGAs. Anxiolytic medications were most common among initiators of quetiapine (25%) and olanzapine (22%) with lower rates among initiators of aripiprazole (15%) and risperidone (10%). A similar pattern was observed for mood stabilizers.

Differences in rates of somatic comorbidities/medical care encounters and somatic medication classes between youth initiating different SGAs were generally smaller than those described for psychiatric diagnoses and medication classes. Exceptions included OB/GYN and metabolic medical care encounters where risperidone showed lower rates than the other commonly used SGAs (likely a reflection of the lower average age of risperidone initiators), and a higher rate of hypertension among olanzapine initiators (10%) compared to the other agents (2-4%).

Figure 1. Flowchart to Create Study cohort, 2000-2013

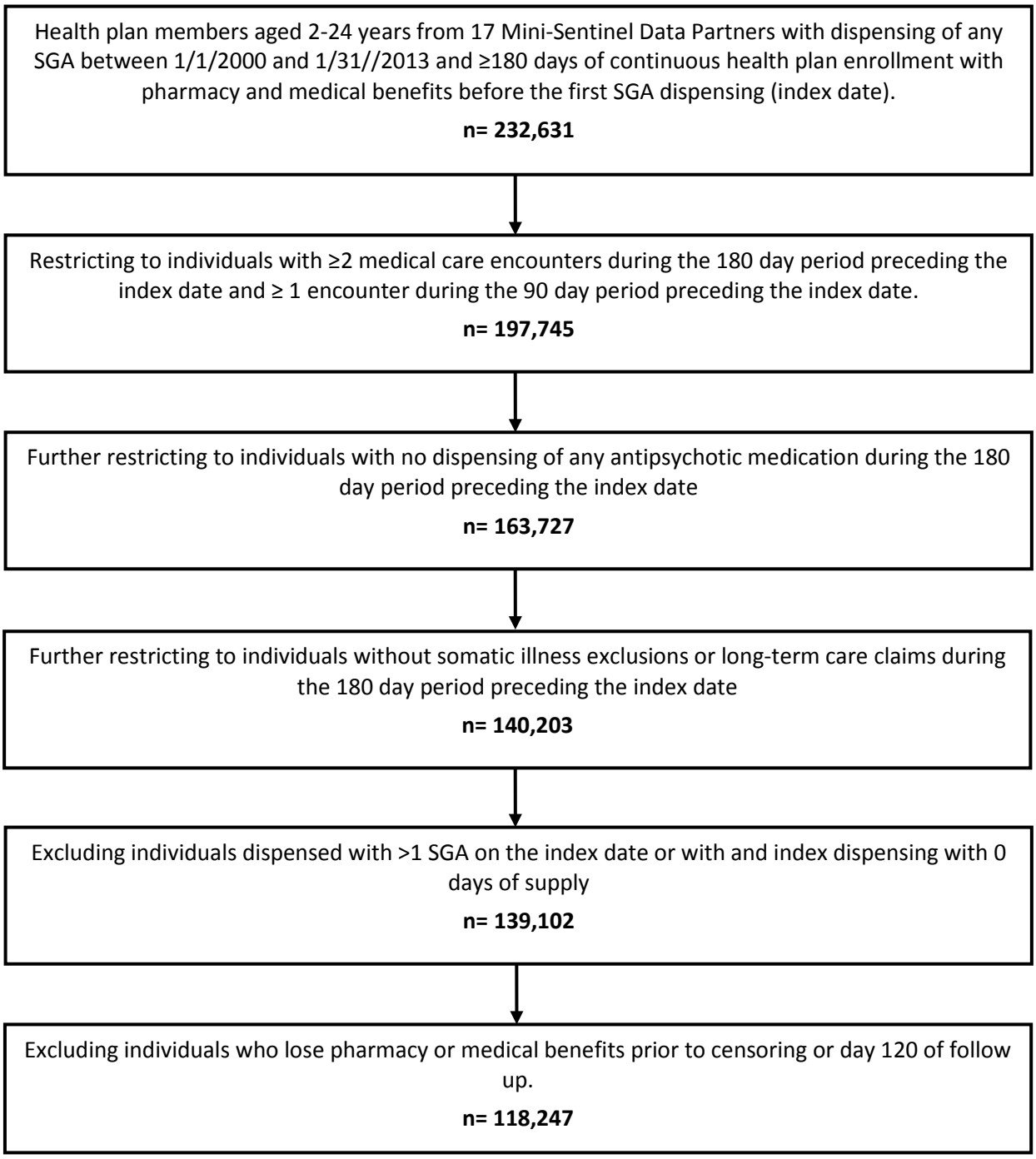


Table 1. Select Baseline Patient Characteristics by SGA, 2000-2012 - Demographics

Characteristics	Aripiprazole (n=33,429)			Quetiapine (n=31,661)			Olanzapine (n=9,719)			Risperidone (n=39,709)	
	N	%	Std. diff.*	N	%	Std. diff.*	N	%	Std. diff.*	N	%
Female sex	17,120	51.2	0.39	16,317	51.5	0.40	3,907	40.2	0.17	12,777	32.2
Age (years)											
2-5	473	1.4	0.29	201	0.6	0.35	52	0.5	0.35	2,894	7.3
6-12	7,320	21.9	0.42	3,369	10.6	0.74	1,038	10.7	0.74	16,349	41.2
13-17	14,252	42.6	0.25	11,697	36.9	0.13	2,976	30.6	0.01	12,255	30.9
18-24	11,384	34.1	0.30	16,394	51.8	0.68	5,653	58.2	0.83	8,211	20.7
Race/Ethnicity											
White	11,396	34.1	0.01	11,270	35.6	0.02	3,486	35.9	0.03	13,731	34.6
Black	1,129	3.4	0.10	1,067	3.4	0.10	470	4.8	0.02	2,129	5.4
Hispanic	864	2.6	0.00	742	2.3	0.02	226	2.3	0.02	1,056	2.7
Other/unknown	20,040	59.9	0.05	18,582	58.7	0.03	5,537	57.0	0.01	22,793	57.4
Index SGA Dose											
≤75mg CPZ	20,126	60.2	0.39	7,215	22.8	0.40	6,920	71.2	0.64	16,343	41.2
>75mg CPZ	12,602	37.7	0.29	24,446	77.2	0.54	2,797	28.8	0.49	20,697	52.1

* Standardized difference, compared with risperidone.

Table 2. Select Baseline Patient Characteristics by SGA, 2000-2012 – Diagnoses/Medical Care Encounters†

Diagnosis	Aripiprazole (n=33,429)			Quetiapine (n=31,661)			Olanzapine (n=9,719)			Risperidone (n=39,709)	
	N	%	Std. diff.*	N	%	Std. diff.*	N	%	Std. diff.*	N	%
Psychiatric Comorbidities											
Schizophrenia and related psychoses	2,189	6.5	0.16	2,033	6.4	0.16	2,203	22.7	0.32	4,357	11.0
Bipolar disorder	7,688	23.0	0.20	7,771	24.5	0.24	3,169	32.6	0.42	6,018	15.2
Depression and other mood disorders	20,064	60.0	0.35	19,614	62.0	0.39	5,665	58.3	0.31	17,004	42.8
ADHD and disruptive behavior disorders	13,127	39.3	0.24	9,199	29.1	0.46	2,622	27.0	0.51	20,339	51.2
Sleep disorder, not organic	1,374	4.1	0.03	3,228	10.2	0.26	690	7.1	0.16	1,410	3.6
Anxiety disorder/phobia	11,786	35.3	0.14	13,178	41.6	0.27	3,386	34.8	0.13	11,493	28.9
Personality disorders	800	2.4	0.03	1,088	3.4	0.09	499	5.1	0.17	767	1.9
Acute stress, adjustment disorder	4,192	12.5	0.04	3,640	11.5	0.00	1,088	11.2	0.00	4,505	11.3
Substance use disorders	3,628	10.9	0.04	7,486	23.6	0.38	2,404	24.7	0.40	3,884	9.8
Somatoform spectrum disorders	614	1.8	0.01	834	2.6	0.04	324	3.3	0.08	798	2.0
Learning disorder/ developmental delay	1,133	3.4	0.17	629	2.0	0.25	247	2.5	0.22	2,894	7.3
PDD, autism, mental retardation	2,460	7.4	0.25	912	2.9	0.44	365	3.8	0.39	5,968	15.0
Organic Psychosis	20	0.1	0.03	24	0.1	0.02	28	0.3	0.03	56	0.1
Tics	364	1.1	0.04	413	1.3	0.02	128	1.3	0.02	597	1.5
Other	6,191	18.5	0.01	7,598	24.0	0.12	2,972	30.6	0.27	7,579	19.1
Psychiatric Symptoms	549	1.6	0.01	543	1.7	0.01	260	2.7	0.06	709	1.8
Injury, self-inflicted or undetermined intent	794	2.4	0.06	1,081	3.4	0.12	242	2.5	0.07	612	1.5
Somatic Comorbidities/Medical Care Encounters											
OB/GYN and related	6,264	18.7	0.22	7,359	23.2	0.33	1,914	19.7	0.25	4,318	10.9
Metabolic (including screening)	9,047	27.1	0.12	9,697	30.6	0.20	2,935	30.2	0.19	8,751	22.0
Diagnosed Hypertension	663	2.0	0.10	1,327	4.2	0.03	991	10.2	0.26	1,457	3.7
Other Diagnosed CV Disease	3,149	9.4	0.04	3,957	12.5	0.14	1,281	13.2	0.16	3,244	8.2
Respiratory/Allergy	3,829	11.5	0.01	4,050	12.8	0.06	1,147	11.8	0.03	4,362	11.0
Gastro-intestinal	3,894	11.6	0.08	4,735	15.0	0.18	1,254	12.9	0.12	3,673	9.2

Diagnosis	Aripiprazole (n=33,429)			Quetiapine (n=31,661)			Olanzapine (n=9,719)			Risperidone (n=39,709)	
Neurologic/musculoskeletal	12,377	37.0	0.09	13,855	43.8	0.22	3,874	39.9	0.14	13,089	33.0

† for definitions see Table 15 in the project protocol. * Standardized difference, compared with risperidone.

Table 3. Select Baseline Patient Characteristics by SGA, 2000-2012 – Medication Classes†

Medication Class	Aripiprazole (n=33,429)			Quetiapine (n=31,661)			Olanzapine (n=9,719)			Risperidone (n=39,709)	
	N	%	Std. diff.*	N	%	Std. diff.*	N	%	Std. diff.*	N	%
Psychiatric											
Mood Stabilizers	6,577	19.7	0.09	8,137	25.7	0.23	2,526	26.0	0.24	6,471	16.3
Antidepressants	20,008	59.9	0.31	20,386	64.4	0.40	5,715	58.8	0.29	17,720	44.6
ADHD drugs	11,595	34.7	0.21	8,422	26.6	0.39	2,060	21.2	0.53	17,929	45.2
Anxiolytics/hypnotics	5,071	15.2	0.16	7,891	24.9	0.40	2,089	21.5	0.32	3,942	9.9
Other psychiatric	2,099	6.3	0.15	3,398	10.7	0.30	692	7.1	0.18	1,247	3.1
Somatic											
Contraceptives	4,950	14.8	0.30	5,385	17.0	0.36	1,168	12.0	0.22	2,269	5.7
Lipid lowering agents	72	0.2	0.03	87	0.3	0.04	23	0.2	0.04	36	0.1
Other metabolic	486	1.5	0.08	438	1.4	0.07	107	1.1	0.05	264	0.7
Antihypertensive	768	2.3	0.07	1,005	3.2	0.13	260	2.7	0.10	518	1.3
Other CV	68	0.2	0.03	70	0.2	0.04	14	0.1	0.02	30	0.1
Respiratory/Allergy	7,900	23.6	0.01	8,336	26.3	0.07	2,198	22.6	0.01	9,204	23.2
Gastro-intestinal	2,117	6.3	0.05	2,964	9.4	0.16	822	8.5	0.13	2,066	5.2
Neurologic/musculoskeletal	6,092	18.2	0.16	8,988	28.4	0.40	2,224	22.9	0.27	5,011	12.6
Antibiotics	12,059	36.1	0.09	12,233	38.6	0.14	3,270	33.6	0.04	12,691	32.0

† for definitions see Table 15 in the project protocol. * Standardized difference, compared with risperidone.

Table 4. Events, Follow-up, and Type 2 Diabetes Incidence

	Events	Persons	Person-years	Incidence rate per 1,000 person-years	95% Confidence Interval
180-day lookback					
Base Case Analysis	42	118,247	36,982	1.14	0.79-1.48
S 1	42	118,247	37,941	1.11	0.77-1.44
S 2	59	118,247	49,685	1.19	0.88-1.49
S 3	41	118,247	29,817	1.38	0.95-1.80
S 4	47	118,247	50,597	0.93	0.66-1.19
S 5	97	118,247	88,809	1.09	0.87-1.31
S 6	114	118,247	36,964	3.08	2.52-3.65
365 day lookback					
Base Case	23	90,468	28,588	1.47	1.03-1.91
S 1	23	90,468	29,336	1.43	1.00-1.86
S 2	33	90,468	38,412	1.54	1.14-1.93
S 3	23	90,468	23,072	1.78	1.23-2.32
S 4	28	90,468	39,096	1.20	0.86-1.55
S 5	62	90,468	68,833	1.41	1.13-1.69
S 6	74	90,468	28,574	3.99	3.26-4.72
Base Case (180 day lookback)					
Risperidone	11	39,709	14,423	*	*
Aripiprazole	19	33,429	10,257	*	*
Quetiapine	7	31,661	8,929	*	*
Olanzapine	2	9,719	2,393	*	*
Ziprasidone	3	2,987	800	*	*
Other	0	742	179	*	*

(S1) 30 days follow-up added after index AP discontinuation or 2nd APM/APM switch, (S2) 90 days follow-up added after index AP discontinuation, (S3) No days added after index AP discontinuation or 2nd APM/APM switch, (S4) 180 day intent to treat (index exposure carried forward until day 180), (S5) 365 day intent to treat (index exposure carried forward until day 365), (S6) base case with secondary type 2 diabetes definition; *not calculated due to small event numbers

3. Follow-up and Events

Follow up times, numbers of incident cases of Diabetes Mellitus Type 2 and incidence rates of Diabetes Mellitus Type 2 for the primary study cohort as well as all alternate specifications are shown in Table 4. In the primary specification, the cohort accrued 36,982 patient years of follow up with a mean follow up duration of 114 days. In alternate follow-up specifications, follow up ranged from 29,817 years with a mean follow up of 92 days (S3) to 88,809 years with a mean follow up of 274 days (S6). There were a total of 42 new cases of incident type 2 diabetes resulting in an incidence rate of 1.14 (0.79-1.48) cases per 1,000 person years of follow up. The broader, secondary case definition yielded 114 cases over 36,964 person years of follow up for an incidence rate of 3.08 (2.52-3.65) per 1,000 person years. Most events occurred in initiators of aripiprazole (n=19), followed by risperidone (n=11), quetiapine (n=7), ziprasidone (n=3), and olanzapine (n=2). No events were observed in initiators of any of the remaining SGAs. Due to the small numbers, no incidence rates were calculated for individual SGAs. No events were observed for persons aged 2-5 years in any of the specifications. For the primary specification, 10 events occurred among 6-12 year olds, 18 events among 13-17 year olds, and 14 events among 18-24 year olds (Table 5).

Table 5. Incident Cases of Diabetes Mellitus Type 2 by SGA and Age Group

Age group (yrs)	Total	Ari-piprazole	Olanza-pine	Quetia-pine	Risperi-done	Ziprasi-done	Other
180 day lookback, primary case definition							
2-5	0	0	0	0	0	0	0
6-12	10	4	0	1	4	1	0
13-17	18	7	1	4	4	2	0
18-24	14	8	1	2	3	0	0
Total	42	19	2	7	11	3	0
180 day lookback, secondary case definition							
2-5	0	0	0	0	0	0	0
6-12	24	9	1	3	9	2	0
13-17	43	19	3	9	8	4	0
18-24	47	17	4	13	10	3	0
Total	114	45	8	25	27	9	0
365 day lookback, primary case definition							
2-5	0	0	0	0	0	0	0
6-12	4	1	0	1	2	0	0
13-17	13	5	1	2	3	2	0
18-24	6	2	1	1	2	0	0
Total	23	8	2	4	7	2	0

4. Trends and Patterns in SGA Incidence

Figures 2-4 show the incidence proportion of SGA (expressed as new SGA treatment episodes per 1,000 patients) use by calendar year overall and stratified by sex (Figure 2), age group (Figure 3) and Data Partner (Figure 4). Note that the overall rates for each calendar year are based on all Data Partners with complete data for that year so that changes between years may partially reflect changes in contributing Data Partners.

Figure 2. SGA Incidence Proportion by Sex and Calendar Year

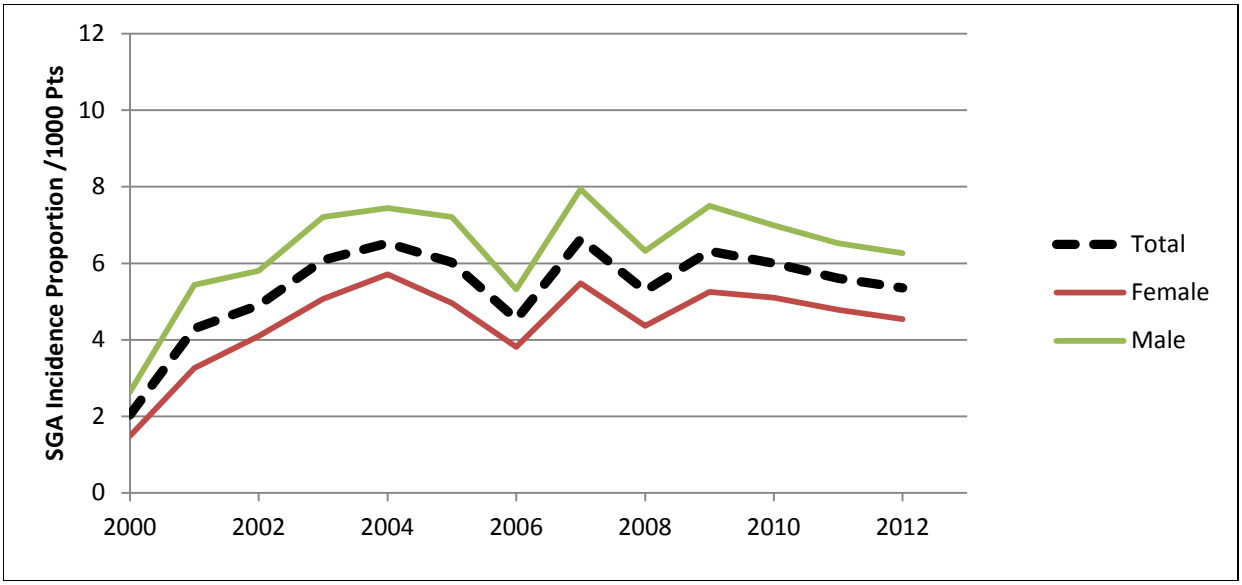
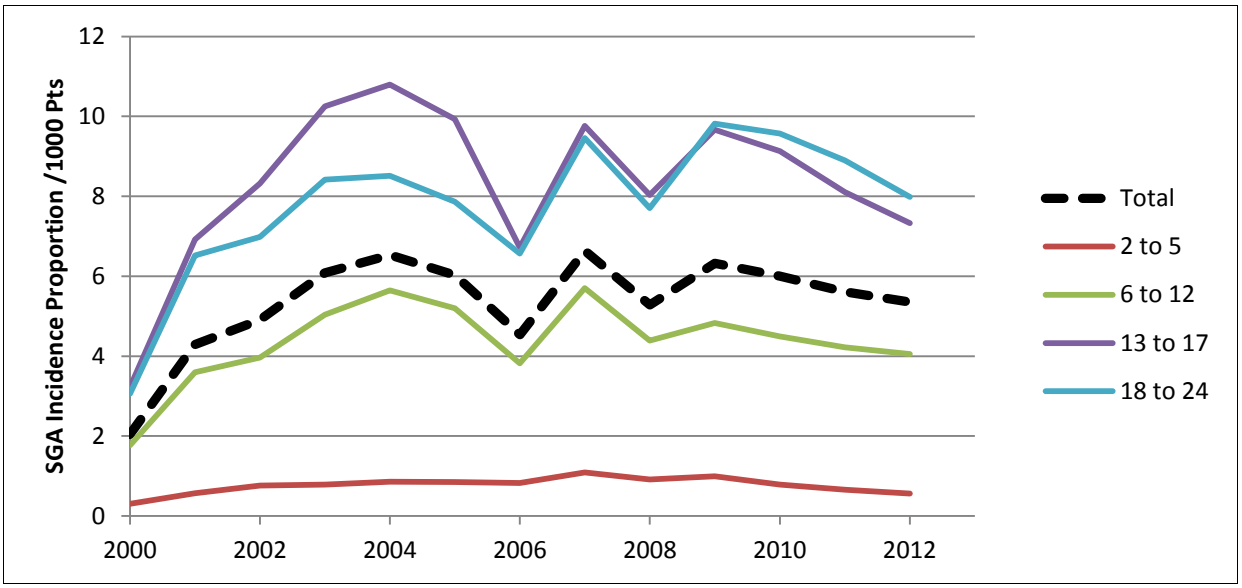


Figure 3. SGA Incidence Proportion by Age Group and Calendar Year



Over the first 4 years of the study period (2000-2004), we observed an increase in SGA use from 2.0/1,000 to 6.1/1,000 followed by largely level use over the remainder of the study period (2005-2012). SGA initiations were more common in males and increased with older age. Two to five year olds showed the lowest initiation rates (at approximately 10-20% of the overall rate), 6-12 year olds showed rates slightly below but close to the overall rate, and 13-17 year olds and 18-24 year olds showed the highest rates (at approximately 150% of the overall use rate) with largely similar rates between the two age groups. By the end of the study period, aripiprazole was the most commonly initiated SGA, followed by risperidone and quetiapine, with markedly lower use rates for olanzapine, ziprasidone and the other SGAs (Figure 5). This distribution was the result of a strong trend away from olanzapine (which was commonly used at the beginning of the study period) and to a lesser degree away from risperidone, and a trend towards quetiapine and particularly aripiprazole.

Figure 4. SGA Incidence Proportion by Data Partner and Calendar Year

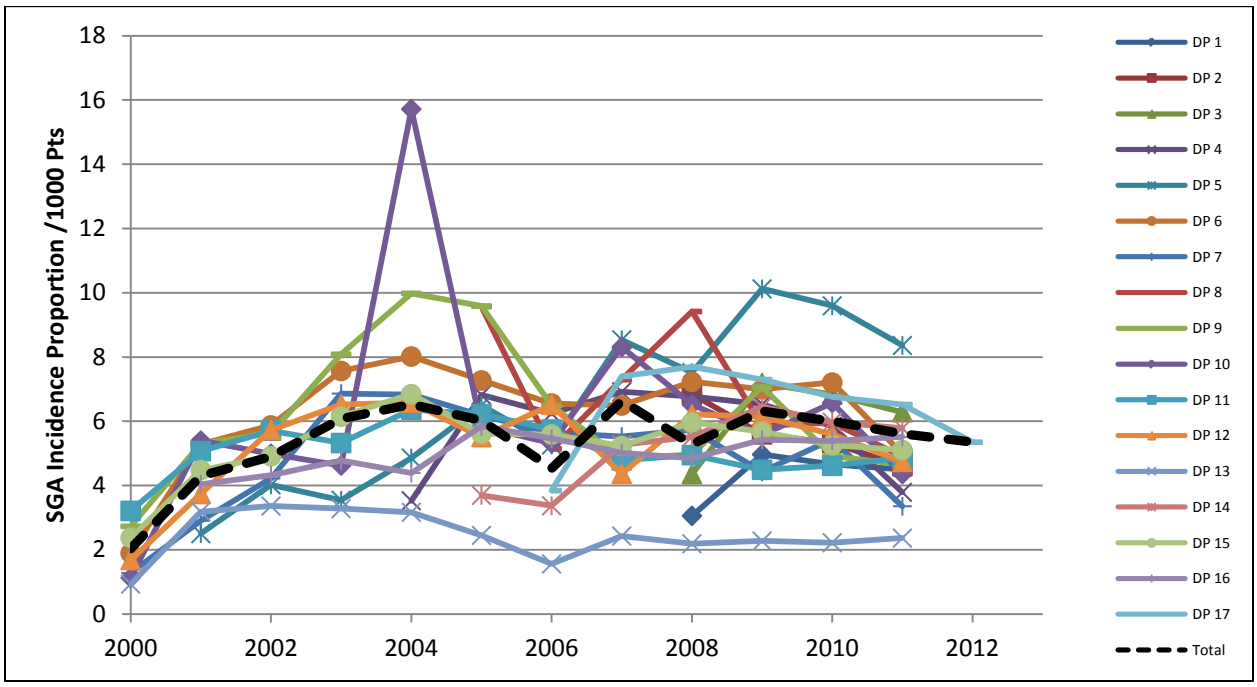
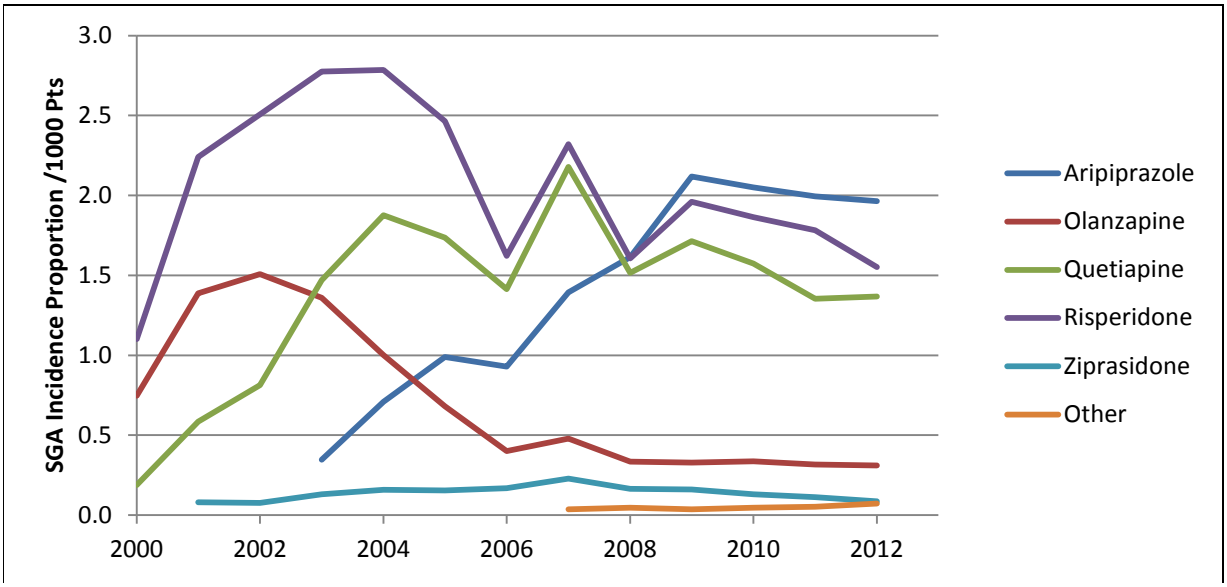


Figure 5. Incidence Proportion by SGA and Calendar Year



C. DISCUSSION

The study identified the largest cohort of privately insured youth with new SGA initiations to date. However, despite including close to 120,000 persons with almost 40,000 person years of accrued follow up, the data –due to the low observed incidence of type 2 diabetes in the study population– did not support the initially planned comparative inferential analyses. The characteristics of the Mini-Sentinel APY cohort were in many ways similar to the prior Medicaid cohort. As in the Medicaid study, significant differences between initiators of individual SGAs in demographic and clinical characteristics highlight the necessity of careful adjustment in any observational comparative study. Distribution of outcome events between individual SGAs differed between the MS and MAX cohorts (in the latter most events occurred in initiators of risperidone, followed by quetiapine, olanzapine, aripiprazole, and ziprasidone). However, due to the small event numbers in the MS cohort and the resulting inability to calculate meaningful adjusted incidence rates or relative risks, inferences regarding the comparison of the results between the two data sources are not supported by the data.

The observed changes in use and use patterns over time are consistent with other reports.[3] We observed a significant increase in incident SGA use from 2000 to 2004 after which the use rates remained relatively stable. Use rates were largely comparable between individual Data Partners and, as expected, varied by sex and age group. After 2005, olanzapine was largely replaced by newer agents (particularly quetiapine and aripiprazole), while risperidone was the most widely used agent over the entire study period. Ziprasidone and the newest atypical agents had only limited use.

1. Limitations

The present study was subject to a number of limitations. First, initially planned SGA-specific incidence rates were not calculated due to low event numbers. For the same reason, the originally specified comparative inferential analyses outlined in the study protocol could not be completed. Instead, a modified work plan two was implemented to generate descriptive data on antipsychotic utilization in the MSDD (see protocol Addendum 1). The lower than expected event numbers in the MS-APY cohort were a result of a lower incidence of type 2 diabetes in the MSDD compared to the MAX data as well as

a smaller cohort size (the initial sample size calculations were based on pharmacy data alone and thus did not require medical coverage, which significantly reduced the size of the cohort). Second, the study made no comparisons to untreated patients or initiators of other psychotropic drug classes, and as such does not support any inferences regarding the potential for an increased type 2 diabetes risk for these contrasts. Third, while the low overall incidence of type 2 diabetes observed in this study is somewhat reassuring, cases may have be missed due to incomplete surveillance as glucose and hemoglobin A1C monitoring rates in youth receiving antipsychotics were concern low. These blood test parameters are the basis of making a type II diabetes diagnosis, unless severe, overt symptoms and signs of diabetes develop, which is relatively rare. Thus, there is a large population with an unmeasured outcome in whom diabetes can neither be verified nor excluded. Fourth, the short follow-up of less than 4 months on average does not allow inferences regarding potential long-term effects, which likely will yield higher rates of this long-term adverse effect and which may follow a different pattern.[13] The lack of longer-term data is especially relevant in young people, as age is inversely related to diabetes risk. Physiologically, youth have a greater pancreatic beta cell reserve than older people, prolonging the time to onset of frank diabetes, which generally develops only after a chronic period of slowly increasing insulin resistance. Fifth, all diagnostic information was based on diagnostic claims of the treating physician, rather than research diagnostic interviews and thus is vulnerable to misclassification. Sixth, exposure to individual SGAs was based on prescription claims and therefore vulnerable to misclassification in patients with non-adherence. Seventh, the MS-wide descriptive trend analyses shown in Figure 2, Figure 3, and Figure 5 present overall rates across individuals from all Data Partners. Because individual Data Partners contribute data for different periods of time (see Appendix 1), any observations of trends and patterns may be partially confounded by changes in contributing Data Partners over time.

2. Conclusions

Small event numbers did not allow inferences regarding the comparative risk for type 2 diabetes between individual SGAs in MSDD youth. We found substantial differences in demographic and clinical characteristics between initiators of individual SGAs. These differences, as well as the observed changes in use patterns over time have to be considered in any future comparative analysis of the safety of SGAs in Youth.

III. SUBPROJECT 2A

A. SPECIFIC AIMS

Explore the feasibility of using BMI and laboratory data available in the MSCDM for baseline confounding adjustment

1. Determine proportion of patients in APY cohort with height and weight data (BMI) available at baseline
2. Determine proportion of patients in APY cohort with baseline HbA1c and/or random or fasting blood glucose (jointly referred to as “GLU”) laboratory results available
3. Characterize and compare proportion of patients with/without baseline height, weight, and/or GLU data
4. Characterize availability of these data elements based on cohort characteristics

B. STUDY SUB-COHORT

The study cohort for exploratory Subproject 2A is entirely nested within the APY cohort developed in Subproject 1 (Table 6), with the earliest cohort entry date of January 1, 2006, the start date of the MSCDM clinical data elements table. The APY Subproject 2A sub-cohort is comprised of patients between the ages of 2 and 24 who newly-initiated a SGA between January 1, 2006 and December 31, 2011 who met the Subproject 1 inclusion and exclusion criteria and from Data Partners who had either clinical laboratory test results (11 of the 17 Data Partners that contributed data to Subproject 1 had clinical laboratory data and 10 of these 11 Data Partners participated in Subproject 2A) or clinical laboratory test results and vital signs (height and weight to calculate body mass index [BMI]; 9 of the 17 Data Partners that contributed data for Subproject 1 had vital signs data and 8 of these 9 Data Partners participated in Subproject 2A) data in the MSCDM data tables.

Table 6 shows MSN Data Partners contributing patients' data to the Subproject 1 cohort and the Subproject 2A sub-cohort.

Table 6. Subprojects 1 and 2A Data Availability in the MSCDM by Data Partner

Data Partner	Contributed to Subproject 1A APY Cohort	Contributed Data to Subproject 2A Sub-Cohort		
		Height/ Weight	HbA1c	Glucose, fasting and/or random
#1	√		√	√
#2	√		√	√
#3	√			
#4	√	√	√	√
#5	√			
#6	√			
#7	√			
#8	√			
#9	√	√	√	√
#10	√	√	√	√
#11	√	√	√	√
#12	√	√	√	√
#13	√	√	√	√
#14	√	√	√	√
#15	Did not participate in this Workgroup activity			
#16	√	√	√	√
#17	√			

C. EXPOSURE ASSESSMENT

The definition and assessment of new initiation of a SGA for Subproject 2A is the same as used in Subproject 1. The index date is the date of first dispensing of the newly-initiated SGA.

D. CRUDE OUTCOME ASSESSMENT

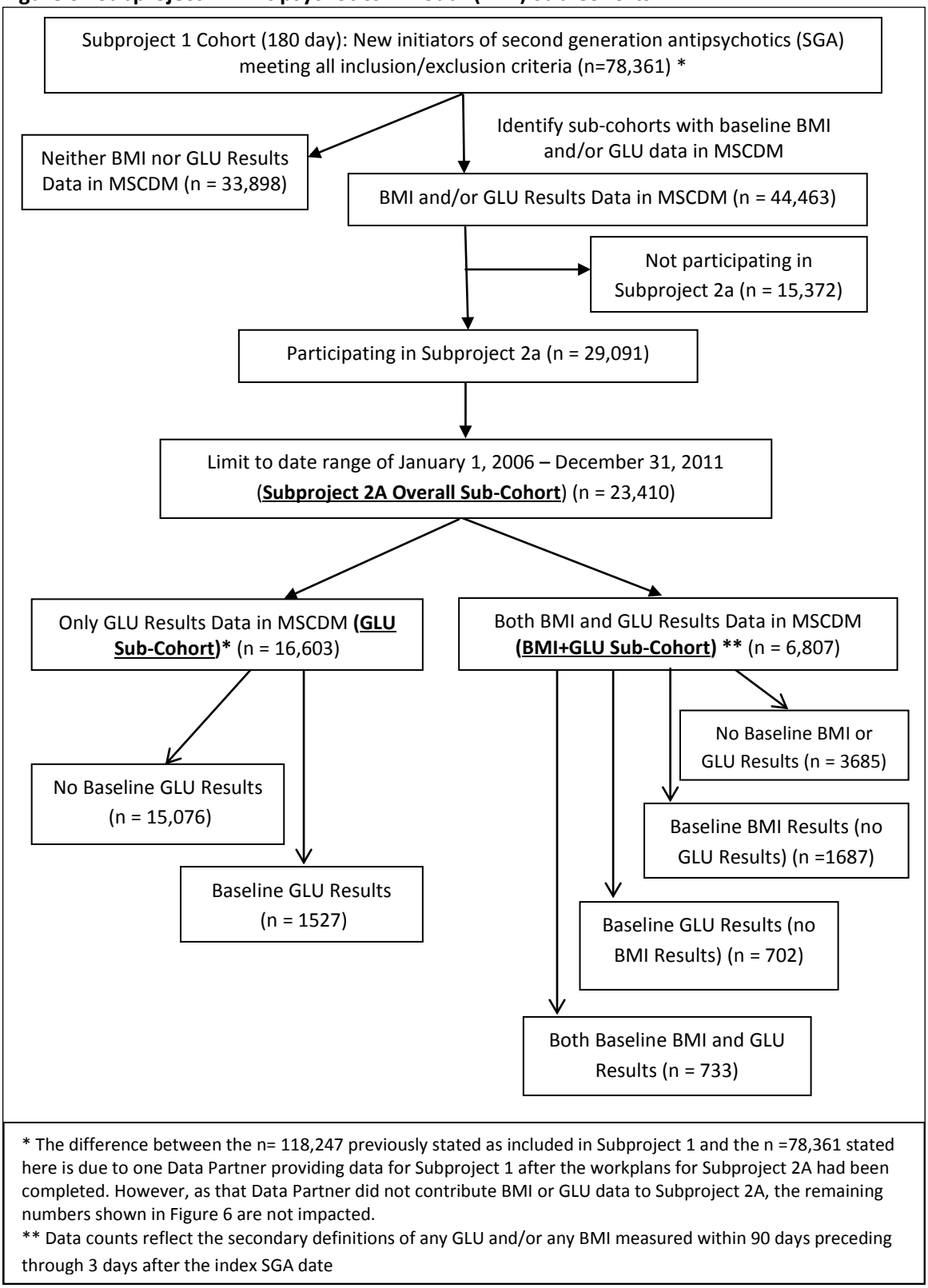
The "outcome" of interest is the presence (and frequency) or absence of BMI and clinical laboratory test results indicating blood glucose monitoring among APY sub-cohort members. For the purposes of this

work, blood glucose monitoring can be any or all of the following: glycosylated hemoglobin (HbA1c), fasting glucose, random glucose, collectively referred to as “GLU.”

BMI and GLU monitoring at baseline (relative to SGA initiation) are the outcomes of interest in Subproject 2A. The number of APY cohort members with the possibility of having BMI results and/or GLU results data in the MSCDM is lower than the total number of individuals in the APY cohort overall. This is in part because only a subset of Data Partners can provide BMI or laboratory results data in the MSCDM and partly because the date for which BMI and laboratory results data first are available in the MSCDM is January 1, 2006. Therefore, the count of all members entering the APY cohort between January 1, 2006 and December 31, 2011 was identified at each Data Partner and summed across Data Partners (Figure 6). Next, the count of members in the APY cohort at each Data Partner with GLU or with GLU+BMI results data in the MSCDM was determined. These counts were summed across Data Partners to yield the denominators of the APY GLU and the APY BMI+GLU sub-cohorts for Subproject 2A (Figure 6).

Figure 6 shows the cohorts and sub-cohorts of individuals in the Subproject 2A project with and without GLU or with GLU+BMI results data in the MSCDM.

Figure 6. Subproject 2A Antipsychotics in Youth (APY) Sub-Cohorts



* The difference between the n= 118,247 previously stated as included in Subproject 1 and the n =78,361 stated here is due to one Data Partner providing data for Subproject 1 after the workplans for Subproject 2A had been completed. However, as that Data Partner did not contribute BMI or GLU data to Subproject 2A, the remaining numbers shown in Figure 6 are not impacted.

** Data counts reflect the secondary definitions of any GLU and/or any BMI measured within 90 days preceding through 3 days after the index SGA date

2A

Height and weight data needed to compute BMI, as well as HbA1c and fasting/random blood glucose data for this sub-cohort was requested from the participating Data Partners. This step provided both the outcomes results data to be explored (presence of GLU laboratory test results data and BMI data) and the crude numerators of APY BMI+BLU and APY GLU sub-cohort members with at least one BMI (or weight only) and/or GLU monitoring event.

E. OUTCOME DATA EXPLORATION

Distributed SAS code were developed, tested, quality checked, and implemented to return the data needed for the crude outcome assessment. Implementing the programming code also resulted in return of the data files needed to explore the completeness and timing of BMI and GLU data relative to the index SGA dispensing date.

Although the SAS programs accessed individual-level data at the participating Data Partners, the code was written such that only relative dates were returned for analysis to maintain deidentified data. All BMI or GLU result dates were calculated relative to the index SGA dispensing date for each sub-cohort member. In the dataset returned for analysis, all BMI and GLU result dates were identified only by the number of days prior to or after (relative to) the index date; only the year of the index date was saved in the shared data.

1. Exploration of Baseline BMI Results Data Availability, Completeness and Timing

a. Definitions

In addition to completing the crude outcome assessment of data availability detailed above, the height and weight results data obtained on the date(s) closest to the index date (i.e., date of SGA initiation) were explored to assess the availability of BMI data according to each of the following definitions:

Primary Definition: Numbers and proportion of members of the sub-cohort with baseline height and weight taken on:

1. The same day and within the date range inclusive of -31 (31 days prior to) through +3 days (3 days after) of index date.

Secondary Definitions: Numbers and proportion of members of the APY sub-cohort with baseline height and weight taken on:

2. The same day and within the date range of -60 through +3 days of index date.
3. The same day and within the date range of -90 through +3 days of index date.
4. Different days and within the date range of -31 through +3 days of index date.
5. Different days and within the date range of -60 through +3 days of index date.
6. Different days and within the date range of -90 through +3 days of index date.
7. The same or different days and within the date range of -31 through +31 days of index date.
8. The same or different days and within the date range of -60 through +31 days of index date.
9. The same or different days and within the date range of -90 through +31 days of index date

Tertiary Definitions: Applying definitions 1 – 3 and 7 – 9 above, determine the additional members of the sub-cohort that would be included if only baseline weight (no height) was required.

b. Results

Results demonstrated that there were n = 6807 members in this sub-cohort between January 1, 2006 and December 31, 2011 for whom BMI results data could have been available in the MSCDM (Figure 6); 16% to 18% entered the cohort each calendar year. Fifty-five percent were male, 45% female. The most common SGA initiated in this sub-cohort was risperidone (43%), followed by quetiapine (27%), aripiprazole (21%), olanzapine (7%) and other (2%). The age distribution of the sub-cohort was as follows: 1% ages 2-4 years, 13% ages 5-9, 10% ages 10-12, 21% ages 13-15, 24% ages 16-18, and 30% ages 19-24.

Detailed results of BMI data availability, timing, and completeness are presented in Tables 7-11. Twenty-one percent of the sub-cohort had BMI available with height and weight obtained on the same day between days -31 and +3 of the index dispensing date, increasing to 36% of the sub-cohort with BMI available with height and weight obtained between -90 through +3 days (Table 7). Essentially all youth had height and weight obtained the same day (n = 2416 for same day and n = 2420 for same or different days). Youth with a height and weight obtained on different days were principally those who had a second weight measured an additional, different, day. Considering only weight (no height measurement requirement), 58% had a weight obtained between days -90 and +3. The proportion with BMI or with only weight measured at baseline varied by Data Partner site.

Table 7. BMI and Weight Data Availability at Baseline Across all AP Agents by Data Partner

Measurement Timeframe	DP4 n = 1582 (23%)	DP 9 n = 240 (4%)	DP 10 n = 306 (4%) *	DP 11 n = 1044 (15%)	DP 12 n = 639 (9%)	DP 13 n = 272 (4%)	DP 14 n = 1337 (20%)	DP 16 n = 1387 (20%)	Total n = 6807
BMI (Height and weight) measured relative to AP index date (%)									
Same day, -31 through +3	242 (15)	94 (39)	1 (<1)	249 (24)	198 (31)	62 (23)	208 (16)	362 (25)	1416 (21)
Same day, -60 through +3	324 (21)	116 (48)	8 (3)	368 (35)	273 (43)	88 (32)	320 (24)	493 (36)	1990 (29)
Same day, -90 through +3	397 (25)	133 (55)	12 (4)	453 (43)	309 (48)	106 (39)	406 (30)	600 (43)	2416 (36)
Different days, -31 through +3	27 (2)	11 (5)	0	25 (2)	18 (3)	10 (4)	25 (2)	65 (5)	181 (3)
Different days, -60 through +3	62 (4)	30 (13)	2 (<1)	54 (5)	32 (5)	23 (9)	63 (5)	128 (9)	394 (6)
Different days, -90 through +3	104 (7)	49 (20)	6 (2)	77 (7)	52 (8)	36 (13)	101 (8)	201 (15)	626 (9)
Same or different days, -31 through +3	242 (15)	94 (39)	1 (<1)	249 (24)	199 (31)	62 (23)	208 (16)	363 (26)	1418 (21)
Same or different days, -60 through +3	325 (21)	116 (48)	8 (3)	368 (35)	274 (43)	88 (32)	321 (24)	494 (36)	1994 (29)
Same or different days, -90 through +3	398 (25)	133 (55)	12 (4)	453 (43)	310 (49)	106 (39)	407 (30)	601 (43)	2420 (36)
Weight measured relative to AP index date (%)									
Day -31 through +3	502 (32)	144 (60)	15 (5)	384 (37)	263 (41)	131 (48)	442 (33)	709 (51)	2590 (38)
Day -60 through +3	640 (41)	163 (68)	25 (8)	529 (51)	357 (56)	168 (62)	633 (47)	886 64)	3401 (50)
Day -90 through +3	739 (47)	179 (75)	31 (10)	633 (61)	397 (62)	188 (69)	771 (58)	1015 (73)	3953 (58)

* At the time the data were extracted for this work, not all patient identifiers were linking correctly across the administrative and BMI data at this Data Partner. The result is that, at this site, rates of BMI and weight only availability are falsely low from this data pull. In the most recent data refresh at this Data Partner this issue has been resolved; future BMI data extractions are expected to reveal higher rates of BMI and weight monitoring at this site.

Risperidone had the highest % of youth with BMI measured (25% between days -31 through +3; 40% between days -90 through +3) and weight measured (60% from days -90 through +3) (Table 8). Across the four agents that accounted for 98% of SGA initiators, olanzapine had the lowest proportion with BMI measured (16% between -31 through +3; 26% between -90 through +3) as well as the lowest proportion with weight measured (54% between days -90 through +3).

Table 8. BMI and Weight Data Availability at Baseline across all DP by AP Agent

Measurement Timeframe	Aripiprazole (n =1417)	Olanzapine (n =501)	Quetiapine (n =1842)	Risperidone (n =2908)	Asenapine, Ziprasidone, Paloperidone (n = 139)	Total Across All AP Agents (n = 6807)
BMI (Height and weight) measured relative to AP index date (%)						
Same day, -31 through +3	270 (19)	81 (16)	330 (18)	718 (25)	17 (12)	1416 (21)
Same day, -60 through +3	405 (29)	108 (22)	486 (26)	963 (33)	28 (20)	1990 (29)
Same day, -90 through +3	496 (35)	131 (26)	587 (32)	1164 (40)	38 (27)	2416 (36)
Different days, -31 through +3	30 (2)	12 (2)	62 (3)	75 (3)	2 (1)	181 (3)
Different days, -60 through +3	79 (6)	26 (5)	119 (7)	163 (6)	7 (5)	394 (6)
Different days, -90 through +3	128 (9)	46 (9)	178 (10)	262 (9)	12 (9)	626 (9)
Same or different days, -31 through +3	270 (19)	81 (16)	331 (18)	719 (25)	17 (12)	1418 (21)
Same or different days, -60 through +3	406 (29)	108 (22)	487 (26)	965 (33)	28 (20)	1994 (29)
Same or different days, -90 through +3	497 (35)	131 (26)	589 (32)	1165 (40)	38 (27)	2420 (36)
Weight measured relative to AP index date (%)						
Day -31 through +3	514 (36)	193 (39)	668 (36)	1171 (40)	44 (32)	2590 (38)
Day -60 through +3	708 (50)	236 (47)	895 (49)	1503 (52)	59 (42)	3401 (50)
Day -90 through +3	836 (59)	270 (54)	1029 (56)	1746 (60)	72 (52)	3953 (58)

BMI and weight only measurements varied by age (Table 9): For height and weight measured on the same day between days -31 and +3, the proportion with BMI measured was 27%—31% for children aged 2-12 years, declining to 21% for those 13-15 years, and to 17% for those 16-24 years. When height and weight were measured between -90 and +3 days, the proportion with BMI measured declined steadily by age from 50% among those aged 2-4 to 30% among those aged 19-24. When considering the weight measurements obtained between -90 and +3 days of the index dispensing, the proportion with weight available declined with age, but the decline was not a consistent decline with increasing age: 71% of those aged 2-4 years had a weight measured between days -90 through +3, while 65% of those aged 5-9 had a weight measured, and across those aged 10-24 years, all age categories had between 56% and 58% with a baseline weight measured.

Table 9. BMI and Weight Data Availability at Baseline across all DP by Age Group

Measurement Timeframe	2 -4 Years n = 84 (1%)	5 -9 Years n = 886 (13%)	10 - 12 Years n = 708 (10%)	13 - 15 Years n = 1419 (21%)	16 – 18 Years n = 1640 (24%)	19 – 24 Years n = 2070 (30%)	Total n = 6807
BMI (Height and weight) measured relative to AP index date (%)							
Same day, -31 through +3	23 (27)	278 (31)	180 (25)	296 (21)	282 (17)	357 (17)	1416 (21)
Same day, -60 through +3	34 (41)	357 (40)	252 (36)	421 (30)	421 (26)	505 (24)	1990 (29)
Same day, -90 through +3	42 (50)	421 (48)	296 (42)	516 (36)	524 (32)	617 (30)	2416 (36)
Different days, -90 through +3 *	18 (21)	91 (10)	78 (11)	129 (9)	153 (9)	157 (8)	626 (9)
Same or different days, -31 through +3	23 (27)	278 (31)	180 (25)	296 (21)	282 (17)	359 (17)	1418 (21)
Same or different days, -60 through +3	34 (41)	357 (40)	253 (36)	421 (30)	422 (26)	507 (25)	1994 (29)
Same or different days, -90 through +3	42 (50)	421 (48)	296 (42)	516 (36)	525 (32)	620 (30)	2420 (36)
Weight measured relative to AP index date (%)							
Day -31 through +3	40 (48)	407 (46)	271 (38)	535 (38)	585 (36)	752 (36)	2590 (38)
Day -60 through +3	54 (64)	504 (57)	355 (50)	712 (50)	784 (48)	992 (48)	3401 (50)
Day -90 through +3	60 (71)	575 (65)	395 (56)	824 (58)	942 (57)	1157 (56)	3953 (58)
* Data not shown for “different days -31 through +3” for “different days -60 through +3” due to small cell sizes in some cells							

As shown in Table 10, the proportion of females and males with BMI measurements available were similar.

Table 10. BMI and Weight Data Availability at Baseline across all DP by Gender

Measurement Timeframe	Female n = 3072 (45%)	Male n = 3735 (55%)	Total n = 6807
BMI (Height and weight) measured relative to AP index date (%)			
Same day, -31 through +3	626 (20)	790 (21)	1416 (21)
Same day, -60 through +3	910 (30)	1080 (29)	1990 (29)
Same day, -90 through +3	1110 (36)	1306 (35)	2416 (36)
Different days, -31 through +3	103 (3)	78 (2)	181 (3)
Different days, -60 through +3	214 (7)	180 (5)	394 (6)
Different days, -90 through +3 *	334 (11)	292 (8)	626 (9)
Same or different days, -31 through +3	627 (20)	791 (21)	1418 (21)
Same or different days, -60 through +3	912 (30)	1082 (29)	1994 (29)
Same or different days, -90 through +3	1113 (36)	1307 (35)	2420 (36)
Weight measured relative to AP index date (%)			
Day -31 through +3	1227 (40)	1363 (37)	2590 (38)
Day -60 through +3	1623 (53)	1778 (48)	3401 (50)
Day -90 through +3	1891 (62)	2062 (55)	3953 (58)

In 2006 (Table 11), 17% of those entering the sub-cohort had a baseline BMI measurement between -31 and +3 days of the index dispensing. Other years: 18% in 2007, 19% in 2008, 21% in 2009, 26% in 2010, and 24% in 2011. In 2006, 29% of those entering the sub-cohort had a baseline BMI measurement between -90 and +3 days of the index dispensing, increasing to 32% in 2007, 31% in 2008, 34% in 2009, 45% in 2010, and 42% in 2011. Weight was measured between -90 and +3 days of the index AP dispensing for 58% in 2006, 55% in 2007, 56% in 2008, 57% in 2009, 64% in 2010, and 60% in 2011.

Table 11. BMI and Weight Data Availability at Baseline across all DP by Index Year

BMI	2006 n =1089 16%)	2007 n = 1157 (17%)	2008 n = 1161 (17%)	2009 n = 1219 (18%)	2010 n = 1111 (16%)	2011 n = 1070 (16%)	Total n = 6807
BMI (Height and weight) measured relative to AP index date (%)							
Same day, -31 through +3	188 (17)	210 (18)	223 (19)	251 (21)	290 (26)	254 (24)	1416 (21)
Same day, -60 through +3	252 (23)	299 (26)	313 (27)	346 (28)	413 (37)	367 (34)	1990 (29)
Same day, -90 through +3	319 (29)	369 (32)	359 (31)	415 (34)	502 (45)	452 (42)	2416 (36)
Different days, -31 through +3	25 (2)	28 (2)	24 (2)	29 (2)	36 (3)	39 (4)	181 (3)
Different days, -60 through +3	58 (5)	67 (6)	62 (5)	61 (5)	72 (7)	74 (7)	394 (6)
Different days, -90 through +3	95 (9)	113 (10)	93 (8)	102 (8)	112 (10)	111 (10)	626 (9)
Same or different days, -31 through +3	188 (17)	210 (18)	223 (19)	251 (21)	290 (26)	256 (24)	1418 (21)
Same or different days, -60 through +3	253 (23)	300 (26)	313 (27)	346 (28)	413 (37)	369 (35)	1994 (29)
Same or different days, -90 through +3	320 (29)	369 (32)	359 (31)	416 (34)	502 (45)	454 (42)	2420 (36)
Weight measured relative to AP index date (%)							
Day -31 through +3	418 (38)	423 (37)	425 (37)	455 (37)	461 (42)	408 (38)	2590 (38)
Day -60 through +3	533 (49)	547 (47)	557 (48)	605 (50)	616 (55)	543 (51)	3401 (50)
Day -90 through +3	626 (58)	639 (55)	644 (56)	692 (57)	714 (64)	638 (60)	3953 (58)

There appears to be a trend towards measuring BMI in a higher proportion of youth at initiation of SGA therapy in more recent years. Weight measurement only did not show the same increase.

2. Exploration of Baseline HbA1c, Fasting Glucose, and Random Glucose Data Availability, Completeness, and Timing

a. Definitions

In addition to completing the crude outcome assessment of data availability, we used the GLU data obtained at baseline -- on the date(s) closest to the index date -- and within the hierarchy of HbA1c > fasting glucose > random glucose to explore the availability of GLU data according to each of the definitions provided below. If two GLU result values were obtained on days equally distant from the index SGA dispensing date (e.g., results obtained 1 day pre-index and also 1 day post-index), the pre-

index result value was used, applied after the hierarchy of HbA1c > fasting glucose > random glucose was applied.

Primary Definitions: Numbers and proportion of members of the sub-cohort with baseline GLU data obtained on:

1. HbA1c obtained between -14 days and +3 days of index date.
2. Fasting glucose obtained between -14 and +3 days of index date.
3. Random glucose obtained between -14 days and +3 days of index date.

Secondary Definitions: Numbers and proportion of members of the sub-cohort with baseline GLU data obtained on:

4. HbA1c obtained between -45 and +3 days of index date.
5. Fasting glucose obtained between -45 and +3 days of index date.
6. Random glucose obtained between -45 and +3 days of index date.
7. HbA1c obtained between -90 and +3 days of index date.
8. Fasting glucose obtained between -90 and +3 days of index date.
9. Random glucose obtained between -90 and +3 days of index date.

b. Results

Results revealed that there were n = 23,410 members in this sub-cohort for whom any available GLU data had been incorporated into the MSCDM (Figure 6), comprised of 44% female and 56% male. Results demonstrated that, in this sub-cohort, risperidone was the most common SGA initiated (36%), followed by aripiprazole (30%), quetiapine (26%), olanzapine (6%), and others (3%). The age distribution of this sub-cohort was 2% ages 2-4 years, 15% ages 5-9, 12% ages 10-12, 18% ages 13-15, 23% ages 16-18, and 30% ages 19-24. The % entering this laboratory test availability sub-cohort was differential by year, with 5% entering in 2006, 5% entering in 2007, 20% entering in 2008, 28% entering in 2009, 23% entering in 2010, and 20% entering 2011.

Detailed results of GLU results data availability, timing, and completeness are presented in Tables 12-16. Only 6% of the sub-cohort had any baseline GLU measurement available based on the primary definition timeframe of -14 through +3 days relative to SGA initiation (range: 2%-19% across Data Partner sites)(Table 12). Applying the broader timeframe definition of -90 through +3 days, any GLU availability averaged 13%, and ranged from 7% to 29% across Data Partners. HbA1c was least often measured at all Data Partners. For all but one DP (DP #11) the majority of GLU measures were random glucose. For DP #11 proportions of fasting and random glucose were similar. Even extending the timeframe to a 365 days look back (-365 through +3 days) only yielded 22% of the sub-cohort with any GLU measurement. Availability of GLU results data varied by type of Data Partner, with integrated healthcare delivery systems/electronic medical records (EHR) sites (DP #4, 9-14, and 16) having 21% with any GLU result and 9% of sub-cohort members from large commercial insurers (DP #1 and 2) having any GLU result in the -90 through +3 day timeframe.

Table 12. Glucose Data Availability at Baseline Across all SGA by Data Partner

Days Relative to SGA Initiation	GLU Category *	DP1 n=14,408 (62%)	DP2 n=2195 (9%)	DP4 n=1582 (7%)	DP 9 n=240 (1%)	DP 10 n=306 (1%) **	DP 11 n=1044 (4%)	DP 12 n=639 (3%)	DP 13 n=272 (1%)	DP 14 n=1337 (6%)	DP 16 n= 1387 (6%)	Total n=23,410
-14 through +3	HgbA1C	50 (<1)	2 (<1)	35 (2)	0 (0)	0 (0)	3 (<1)	26 (4)	5 (2)	4 (<1)	13 (<1)	138 (<1)
	Fasting	72 (<1)	2 (<1)	24 (2)	3 (1)	0 (0)	119 (11)	15 (2)	4 (1)	56 (4)	63 (5)	358 (2)
	Random	396 (3)	58 (3)	95 (6)	27 (11)	6 (2)	73 (7)	49 (8)	35 13)	50 (4)	134 (10)	923 (4)
	Any GLU	518 (4)	62 (3)	154 (10)	30 (13)	6 (2)	195 (19)	90 (14)	44(16)	110 (8)	210 (15)	1419 (6)
	No glucose	13890(96)	2133(97)	1428(90)	210 (88)	300(98)	849 (81)	549(86)	228(84)	1227(92)	1177(85)	21991(94)
-45 through +3	HgbA1C	97 (<1)	6 (<1)	37 (2)	0 (0)	0 (0)	5 (1)	29 (5)	10 (4)	9 (<1)	15 (1)	208 (<1)
	Fasting	137 (1)	3 (<1)	29 (2)	3 (<1)	0 (0)	142 (14)	17 (3)	8 (3)	82 (6)	75 (5)	496 (2)
	Random	727 (5)	93 (4)	130 (8)	45 (19)	14 (5)	109 (10)	66 (10)	44 (16)	85 (6)	193 (14)	1506 (6)
	Any GLU	961 (7)	102 (5)	196 (12)	48 (20)	14 (5)	256 (25)	112 (18)	62 (23)	176 (13)	283 (20)	2210 (9)
	No glucose	13447 (93)	2093(95)	1386(88)	192 (80)	292 (95)	788 (76)	527 (83)	210 (77)	1161(87)	1104(80)	21200(91)
-90 through +3	HgbA1C	133 (<1)	14 (<1)	40 (3)	0 (0)	0 (0)	6 (1)	32 (5)	11 (4)	15 (1)	21 (2)	272 (1)
	Fasting	190 (1)	3 (<1)	32 (2)	5 (2)	0 (0)	155 (15)	19 (3)	10 (4)	115 (9)	90 (7)	619 (3)
	Random	1043 (7)	144 (7)	157 (10)	60 (25)	20 (7)	141 (14)	85 (13)	50 (18)	127 (10)	244 (18)	2071 (9)
	Any GLU	1366 (9)	161 (7)	229 (14)	65 (25)	20 (7)	302 (29)	136 (21)	71 (26)	257 (19)	355 (26)	2962 (13)
	No glucose	13042 (91)	2034(93)	1353(86)	175 (73)	286 (94)	742 (71)	503 (79)	201 (74)	1080(81)	1032(74)	20448(87)
-365 through +3	HgbA1C	271 (2)	30 (1)	48 (3)	2 (1)	1 (<1)	10 (1)	41 (6)	14 (5)	30 (2)	44 (3)	491 (2)
	Fasting	387 (3)	5 (<1)	37 (2)	6 (3)	0 (0)	205 (20)	25 (4)	19 (7)	226 (17)	129 (9)	1039 (4)
	Random	2024 (14)	286 (13)	239 (15)	92 (38)	40 (13)	195 (19)	132 (21)	63 (23)	221 (17)	341 (25)	3633 (16)
	Any GLU	2682 (19)	321 (15)	324 (20)	100 (42)	41 (13)	410 (39)	198 (31)	96 (35)	477 (36)	514 (37)	5163 (22)
	No glucose	11726 (81)	1874(85)	1258(80)	140 (58)	265 (80)	634 (61)	441 (69)	176 (65)	860 (64)	873 (63)	18247(78)

* GLU data are summarized following a hierarchy considering HgbA1C availability first, then Fasting Glucose (Fasting), then Random Glucose (Random). 'Any GLU' indicates a measure for any of the three GLU laboratory tests. Percentages with 'No glucose' indicate no measure for any of the three glucose lab types.

** At the time the data were extracted for this workgroup activity, not all patient identifiers were linking correctly across the administrative and BMI data at this DP site. The result is that, at this site, rates of BMI and weight only availability are falsely low from this data pull. In the most recent data refresh at this DP this issue has been resolved; future BMI data extractions are expected to reveal higher rates of BMI and weight monitoring at this DP site.

As having any GLU measurement available was not common, the broadest timeframe (-90 through +3 days) relative to SGA initiation used in the Secondary Definitions is the timeframe of reference for the rest of this results narrative. Across individual SGA, having any GLU measure availability ranged from 12% to 17% (Table 13) with olanzapine having the highest proportion with any GLU measurement (17%) and risperidone, although comprising the largest % of the sub-cohort (36%) had the lowest % of any GLU data available (12%).

Table 13. Glucose Data Availability at Baseline across all Data Partners by Specific SGA

Days Relative to SGA Initiation	Glucose Category	Aripiprazole n =7043 (30%)	Olanzapine n =1358 (6%)	Quetiapine n =6024 (26%)	Risperidone n =8319 (36%)	Other AP Agents * n = 666 (3%)	Total n =23410
-14 though +3	HgbA1C	50 (<1)	6 (<1)	23 (<1)	58 (<1)	1 (<1)	138 (<1)
	Fasting	100 (1)	13 (1)	68 (1)	175 (2)	2 (<1)	358 (2)
	Random	247 (4)	92 (7)	252 (4)	313 (4)	19 (3)	923 (4)
	Any GLU	397 (6)	111 (8)	343 (6)	546 (7)	22 (3)	1419 (6)
	No glucose	6646 (94)	1247 (92)	5681 (94)	7773 (93)	644 (97)	21991(94)
-45 through +3	HgbA1C	81 (1)	9 (<1)	38 (<1)	78 (<1)	2 (<1)	208 (<1)
	Fasting	145 (2)	21 (2)	102 (2)	222 (3)	6 (1)	496 (2)
	Random	417 (6)	140 (10)	433 (7)	476 (6)	40 (6)	1506 (6)
	Any GLU	643 (9)	170 (13)	573 (10)	776 (9)	48 (7)	2210 (9
	No glucose	6400 (91)	1188 (86)	5451 (91)	7543 (91)	618 (93)	21200(91)
-90 through +3	HgbA1C	107 (2)	13 (1)	54 (<1)	94 (1)	4 (1)	272 (1)
	Fasting	177 (3)	32 (2)	139 (2)	262 (3)	9 (1)	619 (3)
	Random	615 (8)	189 (14)	587 (10)	623 (8)	57 (9)	2071 (9)
	Any GLU	899 (13)	234 (17)	780 (13)	979 (12)	70 (11)	2962 (13)
	No glucose	6144 (87)	1124 (83)	5244 (87)	7340 (88)	596 (90)	20448(87)
-365 through +3	HgbA1C	186 (3)	27 (2)	120 (2)	144 (2)	14 (2)	491 (2)
	Fasting	317 (4)	54 (4)	273 (5)	375 (5)	20 (3)	1039 (4)
	Random	1070 (15)	278 (20)	1077 (18)	1088 (13)	120 (18)	3633 (16)
	Any GLU	1573 (22)	576 (26)	2347 (24)	2883 (19)	154 (23)	8726 (22)
	No glucose	5470 (78)	999 (74)	4554 (76)	6712 (81)	512 (77)	18247(78)
* Other AP Agents include: Asenapine, Ziprasidone, Paloperidone, Iloperidone, and Lurasidone							

Having any baseline GLU measurement varied by age, ranging from 7% for individuals 2-4 Years of age) to 16% among individuals 19-24 years of age, with a steady increase in any GLU availability as age increased (Table 14). Across both genders, 13% of individuals had any GLU measured (14% of females and 12% of males) (Table 15).

Table 14. Glucose Data Availability at Baseline across DP by Age Group

Days Relative to SGA Initiation	Glucose Category	2-4 Years n= 364 (2%)	5-9 Years n=3508 (15%)	10 -12 Years n=2738 (12%)	13-15 Years n= 4282 (18%)	16-18 Years n=5412 (23%)	19-24 Years n=7106 (30%)	Total n= 23410
-14 though +3	HgbA1C Fasting Random Any GLU No glucose	3 (<1) 4 (1) 6 (2) 13 (4) 351 (96)	17 (<1) 55 (2) 91 (3) 163 (5) 3345 (95)	18 (<1) 54 (2) 45 (2) 117 (4) 2621 (96)	27 (<1) 70 (2) 160 (4) 257 (6) 4025 (94)	34 (<1) 86 (2) 234 (4) 354 (7) 5058 (94)	39 (<1) 89 (1) 387 (5) 515 (7) 6591 (93)	138 (<1) 358 (2) 923 (4) 1419 (6) 21991 (94)
-45 through +3	HgbA1C Fasting Random Any GLU No glucose	3 (<1) 4 (1) 14 (4) 21 (6) 343 (94)	22 (<1) 67 (2) 133 (4) 222 (6) 3286 (94)	25 (<1) 68 (3) 83 (3) 176 (6) 2562 (94)	37 (<1) 102 (2) 262 (6) 401 (9) 3881 (91)	52 (1) 119 (2) 402 (7) 573 (11) 4839 (89)	69 (1) 136 (2) 612 (9) 817 (11) 6289 (89)	208 (<1) 496 (2) 1506 (6) 2210 (9 21200 (91)
-90 through +3	HgbA1C Fasting Random Any GLU No glucose	3 (<1) 5 (1) 19 (5) 27 (7) 337 (93)	28 (<1) 79 (2) 178 (5) 285 (8) 3223 (92)	27 (1) 76 (3) 125 (5) 228 (8) 2510 (92)	53 (1) 128 (3) 372 (9) 553 (13) 3729 (87)	71 (1) 151 (3) 543 (10) 765 (14) 4647 (86)	90 (1) 180 (3) 834 (12) 1104 (16) 6002 (85)	272 (1) 619 (3) 2071 (9) 2962 (13) 20448 (87)
-365 through +3	HgbA1C Fasting Random Any GLU No glucose	4 (1) 10 (3) 34 (9) 48 (13) 316 (87)	41 (1) 113 (3) 316 (9) 470 (13) 3038 (87)	47 (2) 106 (4) 236 (9) 389 (14) 2349 (86)	94 (2) 213 (5) 633 (15) 1660 (22) 3342 (78)	120 (2) 251 (5) 955 (18) 1326 (25) 4086 (76)	185 (3) 346 (5) 1459 (21) 1990 (28) 5116 (72)	491 (2) 1039 (4) 3633 (16) 5163 (22) 18247 (78)

Table 15. Glucose Data Availability at Baseline across all DP by Gender

Days Relative to SGA Initiation	Glucose Category	Female n= 10200 (44%)	Male n=13210 (56%)	Total n= 23410
Glucose measured relative to AP index date (%)				
-14 though +3	HgbA1C	61 (<1)	77 (<1)	138 (<1)
	Fasting	166 (2)	192 (2)	358 (2)
	Random	435 (4)	488 (4)	923 (4)
	Any GLU	662 (6)	757 (6)	1419 (6)
	No glucose	9538 (94)	12453 (94)	21991 (94)
-45 through +3	HgbA1C	98 (1)	110 (<1)	208 (<1)
	Fasting	229 (2)	267 (2)	496 (2)
	Random	717 (7)	789 (6)	1506 (6)
	Any GLU	1044 (10)	1166 (9)	2210 (9
	No glucose	9156 (90)	12044 (91)	21200 (91)
-90 through +3	HgbA1C	124 (1)	148 (1)	272 (1)
	Fasting	283 (3)	336 (3)	619 (3)
	Random	1033 (10)	1038 (8)	2071 (9)
	Any GLU	1440 (14)	1522 (12)	2962 (13)
	No glucose	8760 (86)	11688 (89)	20448 (87)
-365 through +3	HgbA1C	228 (2)	263 (2)	491 (2)
	Fasting	525 (5)	514 (4)	1039 (4)
	Random	1861 (18)	1772 (13)	3633 (16)
	Any GLU	2614 (26)	2549 (19)	5163 (22)
	No glucose	7586 (74)	10661 (81)	18247 (78)

Any GLU results availability ranged from 9% to 20% across 2006 to 2011 (Table 16). In 2006, 17% of those entering the sub-cohort had any GLU result available. This rose to 20% in 2007, dropped back to 10% in 2008, and then rose slowly over the remaining years: 2009 = 11%, 2010=13%, and 2011=14%.

Table 16. Glucose Data Availability at Baseline across all DP by Year

Days Relative to SGA Initiation	Glucose Category	2006 n= 1089 (5%)	2007 n= 1237 (5%)	2008 n=4593 (20%)	2009 n= 6452 (28%)	2010 n= 5300 (23%)	2011 n= 4739 (20%)	Total n= 23410
-14 though +3	HgbA1C	3 (<1)	11 (1)	18 (<1)	23 (<1)	49 (1)	34 (1)	138 (<1)
	Fasting	33 (3)	50 (4)	74 (2)	79 (1)	56 (91)	66 (1)	358 (2)
	Random	67 (6)	72 (6)	131 (3)	215 (3)	226 (4)	212 (5)	923 (4)
	Any GLU	103 (9)	133 (11)	223 (5)	317 (5)	331 (6)	312 (7)	1419 (6)
	No glucose	986 (91)	1104 (89)	4370 (95)	6135 (95)	4969 (94)	4427 (93)	21991 (94)
-45 through +3	HgbA1C	3 (<1)	12 (1)	25 (1)	35 (1)	77 (2)	56 (1)	208 (<1)
	Fasting	45 (4)	66 (5)	102 (2)	111 (2)	82 (2)	90 (2)	496 (2)
	Random	95 (5)	123 (10)	222 (5)	357 (6)	361 (7)	348 (7)	1506 (6)
	Any GLU	143 (13)	201 (16)	349 (8)	503 (8)	520 (10)	494 (10)	2210 (9)
	No glucose	946 (87)	1036 (84)	4244 (92)	5949 (92)	4780 (90)	4245 (90)	21200 (91)
-90 through +3	HgbA1C	5 (1)	17 (1)	35 (1)	46 (1)	94 (2)	75 (2)	272 (1)
	Fasting	56 (5)	77 (6)	125 (3)	150 (2)	99 (2)	112 (2)	619 (3)
	Random	119 (11)	148 (12)	322 (7)	506 (8)	490 (9)	486 (10)	2071 (9)
	Any GLU	180 (17)	242 (20)	482 (10)	702 (11)	683 (13)	673 (14)	2962 (13)
	No glucose	909 (84)	995 (80)	4111 (90)	5750 (89)	4617 (87)	4066 (86)	20448 (87)
-365 through +3	HgbA1C	7 (1)	24 (2)	74 (2)	96 (2)	143 (3)	147 (3)	491 (2)
	Fasting	66 (6)	113 (9)	203 (4)	273 (4)	197 (4)	187 (4)	1039 (4)
	Random	161 (15)	232 19)	637 (14)	945 (15)	848 (16)	810 (17)	3633 (16)
	Any GLU	234 (21)	369 (30)	914 (20)	1314 (20)	1188 (22)	1144 (24)	5163 (22)
	No glucose	855 (79)	868 (70)	3679 (80)	5138 (80)	4112 (78)	3595 (76)	18247 (78)

3. Exploration of Baseline HbA1c, Fasting Glucose, and Random Glucose Results Baseline Data Availability, Completeness, and Timing in Conjunction with Baseline BMI Results Data Availability, Completeness, and Timing

By definition, the number of individuals with baseline BMI and baseline GLU results data available could not exceed the number of individuals in the smaller sub-cohort (i.e., the BMI sub-cohort), nor exceed the number of individuals with GLU baseline results data available (Figure 6). Thus, among the n=6807 in the BMI sub-cohort, the number and % with BMI (height and weight measured the same or on different days) who also had any GLU, and who had both BMI and GLU measured at any time between day -90 and +3 relative to the index SGA dispensing was n = 733 (11%) (Figure 6, Table 17). If only weight (not weight and height) was required, then n = 1135 (17%) had baseline weight in conjunction with baseline GLU data available.

Table 17. Baseline BMI and Baseline GLU Results Data Availability across all SGA by DP

BMI or Weight Only and Any GLU	DP with BMI and GLU available (n=6807)								
	DP4 n = 1582 (23%)	DP 9 n = 240 (4%)	DP 10 n = 306 (4%) *	DP 11 n = 1044 (15%)	DP 12 n = 639 (9%)	DP 13 n = 272 (4%)	DP 14 n = 1337 (20%)	DP 16 n = 1387 (20%)	Total n = 6807
BMI same day, -31 through +3 days and any GLU, -14 through +3 days	37 (2)	10 (4)	0 (0)	73 (7)	50 (8)	13 (5)	34 (3)	75 (5)	292 (4)
BMI same or different days and any GLU, both -90 through +3 days	96 (6)	35 (15)	3 (1)	168 (16)	89 (14)	33 (12)	128 (10)	181 (13)	733 (11)
Weight and any GLU, both -90 through +3 days	174 (11)	53 (22)	7 (2)	223 (21)	109 (17)	60 (22)	204 (15)	305 (22)	1135 (17)
* At the time the data were extracted for this work, not all patient identifiers were linking correctly across the administrative and BMI data at this Data Partner. The result is that, at this site, rates of BMI and weight only availability are falsely low from this data pull. In the most recent data refresh at this Data Partner, this issue has been resolved; future BMI data extractions are expected to reveal higher rates of BMI and weight monitoring at this site.									

4. Ascertainment of BMI and Glucose Results Data Availability Up to One Year after SGA Initiation (Pilot data for Subproject 3)

Given the low incidence of diabetes in the Subproject 1 cohort, to assist in determining the feasibility of examining changes in BMI and GLU over time after initiating a SGA as an outcome of interest (Subproject 3), we estimated the availability of BMI and GLU results up to one year (through day +365) after SGA initiation. The information in this section should be considered pilot data, as it is provided to assist in determining whether to conduct Subproject 3, and is not included in tables as it is not part of Subproject 2A results.

Among the n = 6807 in the BMI sub-cohort, at least one post-SGA initiation BMI measurement result is available for n=4654 (68%) (Range across Data Partners: 51% to 82%).

1. Among those with BMI results data available within the year after initiating a SGA, the first weight after SGA initiation was measured by day +90 in n = 3560 (67%), between days +91 and +180 in n= 982 (19%), and between days +181 and +365 in n = 747 (14%).
2. Among those with BMI results data available within the year after initiating a SGA, the first height was measured by day +90 in n = 2168 (52%), between days +91 and +180 in n = 918 (22)% and between days +181 and +365 in n = 1087 (16% (26%).
3. Among those with at least one BMI measurement during the 365 days after initiation of the SGA, across all SGA and all eight Data Partners, n = 1860 (40%) of the sub-cohort have both a baseline BMI and at least one BMI available within one year after SGA initiation, n = 560 (12%) have a baseline BMI but no follow-up BMI available, and n = 2234 (48%) have a follow-up BMI

but no baseline BMI. It is likely that some of the individuals who do not have BMI have weight (only) data available that could be also used for assessing change over time.

Among the n=23,410 in the GLU sub-cohort, post-SGA initiation GLU measurement results are available for n=5883 (25%) (Range across Data Partners: 12% to 48%).

1. Availability of GLU results within the year after SGA initiation varied by type of Data Partner, with integrated healthcare delivery systems/electronic medical records (EHR) sites (DP #4, 9-14, and 16) having 37% of the sub-cohort with any GLU result and large commercial insurers (DP #1 and 2) having 20% of sub-cohort members with any GLU result.
2. Post-SGA initiation GLU measurement availability ranged across SGA from 23% of those initiated on an "other" SGA (i.e., a drug other than olanzapine, risperidone, quetiapine, or aripiprazole) to 29% of those initiated on olanzapine.
3. Post-SGA GLU measurement ranged across age groups from 17% among those ages 2-4 years to 26% to 27% of those ages 13-24 years. Twenty-eight % of females and 23% of males had some GLU measurement post-SGA initiation. By year, having any post-SGA initiation GLU measurement results available in the MSCDM included 16% in 2006, 34% in 2007, 22% in 2008, 23% in 2009, 25% in 2010, and 26% in 2011.
4. Within the same individual, any GLU measurement both prior to and after SGA initiation are available for only n = 2098 (9%) of the sub-cohort; n =2839 (12%) had a GLU measurement only prior to initiating the SGA; n = 3785 (16%) had a GLU measurement only after initiating the SGA.

F. ASSESSMENT OF MISSING DATA AND METHODS TO HANDLE MISSING DATA

The findings of this exploratory work demonstrate that the available GLU and BMI results data can be useful for planning additional efforts, with some limitations.

1. Overall Assessment of Missing Baseline BMI and GLU Results Data

1. When Subproject 2A was planned, the (low) number of diabetes outcomes observed in Subproject 1 was not known.
2. One large Data Partner contributing both BMI and laboratory results data to the MSCDM participated in Subproject 1, but did not participate in Subproject 2A. Similarly, one other large Data Partner with laboratory results data in the MSCDM participated in Subproject 1, but did not participate in Subproject 2A. However, the overall % of the cohort with BMI and/or GLU data at the participating Data Partners is likely representative of the available and missing results data at these two Data Partners.
3. Complete laboratory test and BMI results information is not available on the Data Partner populations at all sites, given that not all Data Partners are staff or group model health plans. This clinical data would not be available for members at Data Partners who are not in the staff/group model component? Regardless, the proportion in the cohort with blood glucose data is low even from the Data Partners that are staff/group model health plans.
4. While it likely does not have much impact in the overall proportion with blood glucose results, finger stick data obtained as point of care results may or may not be captured.
5. The number available for specific drug comparisons is lower than would have been estimated across all sites that participated in Subproject 1.

6. One small DPs BMI data had an error that limited capture and matching of these data to the cohort; this is a small site with little impact on combined site % of available data.

2. Missing Baseline GLU Results Data

1. Any GLU monitoring before initiation of SGA was low across DPs
2. Even with time frame of -90 days through +3 days of SGA initiation, < 20% of sub-cohort had any GLU results data
3. GLU monitoring was low across all DP, by age, and by year of SGA initiation
4. Although availability of baseline GLU results data varied between EHR sites (21% of sub-cohort) and large commercial insurer sites (9% of sub-cohort), even at the EHR Data Partners, baseline GLU monitoring rates were low and it is not clear that monitoring was nonselective.

3. Missing Baseline BMI Results Data

1. Height and weight to calculate BMI was available for a moderate proportion of the sub-cohort (36%) within 90 days preceding the initial SGA index dispensing. Baseline weight (not height) was captured on over half (58%) of this sub-cohort.
2. Most missing data correction techniques rely on assumptions that data are at least Missing At Random (MAR; MAR after accounting for observed, measured covariates). In light of this, the pattern of higher data capture at lower age groups is not surprising and might not be a major concern. However, the differing patterns of BMI and weight availability by drug are problematic and raise questions of selection bias in monitoring.

4. Missing Baseline and Post-SGA Initiation BMI and GLU Results Data

Requiring measurements both pre and post drug initiation, 14% (n=979 of the 6807 from EHR Data Partner sites) had BMI measurements within 90 days on each side of the first SGA dispensing. Allowing up to 365 days after drug initiation, 27% (n=1852) had both pre and post BMI measurements. Weight capture 90 days preceding and up to 365 days after drug initiation was available for 52% of the sub-cohort (n=3552).

G. CONCLUSIONS

With such a small proportion of the Subproject 2A sub-cohort having baseline GLU results, the data are inadequate for use as baseline adjustment covariates. The proportion of individuals in the Subproject 2A sub-cohort with baseline BMI and weight data indicate these data can possibly be useful for targeted baseline confounding adjustment questions, although BMI baseline data are still of limited availability and make such efforts difficult and results less convincing.

Given that 27% (1852 of 6807) of the BMI sub-cohort have both baseline and post-drug initiation BMI measurements and that 52% (3552 of 6807) have both baseline and post-drug initiation weight measurements, analyses evaluating change in these measures over time within individuals is reasonable to consider. However, across individuals with baseline and post-SGA initiation BMI measurements, GLU measurement both prior to and after SGA initiation is available for only 9% of the sub-cohort.

We conclude that, despite the FDA warning regarding the risk of hyperglycemia and diabetes mellitus with all SGAs and recommendations from multiple national organization to conduct metabolic screening

and monitoring with use of SGA, a very low proportion of youth in this study (in the sub-cohort of sites with available data) have either baseline or ongoing assessment of any blood glucose (HbA1c, fasting glucose, or random glucose). We further conclude that, among the sub-cohort of youth in the MSCDM from Data Partners with EHR data, 27% have baseline and follow-up height and weight assessment (i.e., BMI), and that 52% have baseline and follow-up weight assessment.

IV. APPENDICES

A. APPENDIX 1. DATA CONTRIBUTION PERIODS FOR EACH MINI-SENTINEL DATA PARTNER SITE

Data Partner	Data Contribution Period
1	1/1/08 - 9/30/12
2	6/1/07 - 11/30/12
3	1/1/08 - 3/31/12
4	1/1/04 - 12/31/11
5	7/1/00 - 4/30/12
6	1/1/00 - 12/31/11
7	1/1/00 - 12/31/11
8	1/1/00 - 6/30/12
9	1/1/00 - 6/30/12
10	1/1/00 - 12/31/11
11	1/1/00 - 9/30/12
12	1/1/00 - 6/30/12
13	1/1/00 - 10/31/12
14	1/1/05 - 6/30/12
15	1/1/00 - 6/30/12
16	7/1/00 - 6/30/12
17	1/1/06 - 1/31/13

B. APPENDIX 2. COMPUTER CASE DEFINITION FOR DIABETES ACCORDING TO TYPE OF DIABETES-RELATED MEDICAL CARE ENCOUNTER

	Inpatient	*Outpatient*	*Prescription*[b]
Diabetes-Related Medical Care Encounter[a]			
Definition	Inpatient stay with 1) a diagnosis for diabetes (ICD-9-CM: 250, 250.0x, 250.1x, 250.2x, 250.3x, 250.9x)[c]; or 2) an outpatient encounter (including ED) with a primary diagnosis of diabetes during the *hospital stay period*, defined as the day prior to admission through the day following discharge.	Outpatient visit (including ED) with a primary diagnosis of diabetes, excluding those during the hospital stay period.	Filled prescription for any diabetes medication, including insulin, insulin adjuncts (pramlintide), and oral hypoglycemics. There can be no diagnosis, primary or secondary, of polycystic ovarian syndrome in the interval $[t_x\text{-}120, t_x\text{+}120]$
Index date, t_x, initial	t_a (admission date) unless ED/outpatient visit with diabetes diagnosis on t_a-1 in which case t_a-1.	Day of visit	Day of prescription fill
Additional Criteria Required to Meet Criteria for Diabetes Case			
Exclusion[d]	Polycystic Ovarian Syndrome		
Confirmation[d] (primary definition)	Diabetes medication prescription, outpatient diagnosis, inpatient diagnosis	Diabetes medication prescription, inpatient diagnosis	1. Outpatient diagnosis, inpatient diagnosis, or 2. Subsequent prescription, and procedure indicating diabetes management[e], and no diagnosis absent/irregular menses (ICD-9-CM: 626.0x, 626.4x)
Confirmation[d] (secondary definition)	As above or glycosylated hemoglobin test (indicating possible diabetes management).		As above
Index date, final	If diabetes-related procedure[f] in the interval $[t_x\text{-}29, t_x\text{-}1]$ t_x is set to procedure date.		

[a]Does not include deaths as there were none with diabetes coded as an underlying cause of death for cohort members during the study period.
[b]If both a prescription and other encounter on the same day, classified as a prescription encounter.
[c]Does not include ICD-9-CM: 250.4-250.8, which are chronic complications of diabetes and thus unlikely to be present for newly diagnosed cases, particularly in a population of children/youth.
[d]Period for exclusion or confirmation is $[t_x\text{-}120, t_x\text{+}120]$.
[e]Diabetes management: HbA1c (CPT: 83036,83037 , glucose test strips (CPT: A4253), glucose monitor (CPT: E2101,E2100,E0609,E0607, insulin pump (CPT: Y3204,Y3286,Y3264,Y3284,E0784).
[f]Diabetes-related procedure: HbA1c (glycated hemoglobin), islet cell antibody test, insulin RIA, or metabolic panel.
Cases are considered type 1 diabetes (and censored) if there was at least one prescription for insulin within 120 days of the index date, with no more than a single prescription for an oral hypoglycemic (PRAMLINTIDE, METFORMIN, PHENFORMIN, CHLORPROPAMIDE, TOLAZAMIDE, TOLBUTAMIDE, ACETOHEXAMIDE, GYLBURIDE, GLIPIZIDE, ACARBOSE, GLIMEPIRIDE, TROGLITAZONE, REPAGLINIDE, MIGLITOL, ROSIGLITAZONE, PIOGLITAZONE, MATEGLINIDE, EXENATIDE, SITAGLIPTIN) in that interval. The single prescription for an oral agent was allowed because, on occasion, these drugs may be prescribed while awaiting the results of confirmatory testing for type 1 diabetes. Otherwise, the case was classified as type 2 diabetes.

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