SENTINEL ASSESSMENTS

CHANGE IN WEIGHT AT 12 AND 52 WEEKS FOR YOUTH INITIATING TREATMENT WITH SECOND GENERATION ANTIPSYCHOTIC MEDICATIONS

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Sentinel

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I. ABSTRACT

A. OBJECTIVE:

To determine the weight z-score change for outpatients initiating monotherapy with quetiapine, risperidone or aripiprazole between treatment initiation and: (i) 12 (+/- 2) and (ii) 52 (+/- 8) weeks.

B. METHODS:

Retrospective cohort analysis of outpatient youth in the Mini-Sentinel Distributed Database (MSDD) with a new episode of second-generation antipsychotic (SGA) therapy between 01/01/2006 and 12/31/2012 using linear regression modeling to model the change in weight z-score at 12 and 52 weeks and inverse probability weighting to balance the medication exposure groups regarding known confounders available in the MSDD.

C. RESULTS:

There were 3,722 youth aged ≥2 and ≤18 years at 5 sites in the MSDD population with 1,544 missing baseline weight measurements. Among the 1,789 youth who met inclusion criteria, 369 were included in the 12-week outcome analysis (incident users of aripiprazole=64, quetiapine=76, risperidone=229) and 548 in the 52-week analysis (aripiprazole=106, quetiapine=117, risperidone=325) who had baseline and follow-up physical weight measured and who remained on the initiated SGA for the full exposure time. At 12 weeks, the adjusted mean changes in weight z-score were: aripiprazole=0.33 (95% CI=0.18-0.48); quetiapine=0.22 (95%CI=0.08-0.37); risperidone=0.32 (95%CI: =0.21-0.44) and did not differ across the three groups. At 52 weeks, the adjusted mean changes in weight z-score were: aripiprazole=0.37 (95%CI=0.11-0.63); quetiapine=0.13 (95%CI=-0.01-0.27); and risperidone=0.35 (95%CI: =0.23-0.48). Youth taking quetiapine had lower adjusted change in weight z-score at 52 weeks compared to youth taking aripiprazole (β = -0.24, 95% C.I. = -0.44 to -0.03).

D. DISCUSSION:

There was not a statistically significant difference in growth-adjusted change in standardized physical weight between aripiprazole, quetiapine and risperidone at 12 weeks. At 52 weeks, youth taking quetiapine had a statistically significant lower growth-adjusted change in standardized physical weight compared to youth taking aripiprazole or risperidone. Besides intrinsic differences in drug effects, possible reasons for this result may be differences between the drugs in indications, dosages prescribed and treatment adherence, factors that could not be fully modeled using the available data.

E. CONCLUSIONS:

Our results argue for improved monitoring of weight rather than medication selection for youth aged ≥2 and ≤18 years when SGAs are used in ambulatory settings for real-world indications. There is an urgent need to improve monitoring of weight in routine care. Because observed differences at 52 weeks may be due to dosages and treatment adherence, further population-level research on these variables is needed.

II. INTRODUCTION

Use of second generation antipsychotic (SGA) medications is associated with significant weight gain and this weight gain is associated with incident diabetes mellitus, cardiovascular disease, and premature mortality in youth.(1-8) Individual SGAs carry different risks, with clozapine and olanzapine considered most strongly associated with weight gain and aripiprazole and ziprasidone considered the most metabolically neutral.(4, 9, 10) While there have been extensive studies in adults, the magnitude and trajectory of weight gain in youth is less well understood. Studies in youth suggest that SGAs are associated with an absolute increase in body mass index (BMI) percentile between 8% (aripiprazole) and 24% (olanzapine) in the three months following initiation.(11) There is concern that youth may be more vulnerable to the metabolic side effects of these medications and that, with continued treatment, these negative side effects propagate through the lifespan – potentially leading to higher risk of cardiovascular disease and increased premature mortality.(12-15)

Important questions remain unanswered about differential safety of the use of SGAs in younger individuals, particularly the relative differences in weight gain between the medications when used in 'real-world' settings.(16-18) Although there is evidence from adequately powered clinical trials that potential weight gain differs significantly between the SGAs in youth, (9, 19-24) population-level evidence from real-world settings is not available. The overall goal of this project was to determine, via a protocol-based assessment, whether individual SGAs are associated with differential risks of potentially harmful weight gain when taken by children and adolescents in typical outpatient care settings in the United States.

III. METHODS

A. POPULATION

The population of youth included all individuals aged ≥2 and ≤18 years initiating monotherapy with olanzapine, quetiapine, risperidone or aripiprazole between January 1, 2006 and December 31, 2012 (see 1 for approval dates for pediatric indications). Data were extracted from the Mini-Sentinel Distributed Database (MSDD). The MSDD refers to data held and maintained by Data Partners in the Mini-Sentinel Common Data Model (MSCDM) format. The MSCDM was developed in accordance with the MSCDM Guiding Principles and was modeled after the Health Care Services Research Network Virtual Data Warehouse.(25) We assembled data from 5 Data Partners: Kaiser Permanente Hawaii, Group Health Cooperative, Kaiser Permanente Northwest, Kaiser Permanente Colorado, and Kaiser Permanente Mid-Atlantic.

B. INCLUSION CRITERIA

All individuals were required to be new users of aripiprazole, olanzapine, quetiapine, or risperidone. Criteria required continuous enrollment in a health plan with both medical and prescription drug coverage for 365 days preceding baseline, allowing enrollment lapses of ≤45 days. Individuals were aged ≥2 and ≤18 years at initiation of monotherapy with an SGA (baseline). We required a washout period of at least 180 consecutive days before baseline with no dispensed prescriptions for any antipsychotics (i.e., incident users). We required individuals to have at least one medical care encounter (inpatient, emergency department, physician or other outpatient) in the 365 days preceding baseline to capture youth with health system contact. We also required at least one day of study follow-up after SGA

initiation to ensure that there was at least one day of follow-up to measure post initiation censoring, disenrollment, or discontinuation.

C. EXCLUSION CRITERIA

We excluded individuals with missing date of birth or sex and anyone in a long-term care institution or palliative care at baseline or in the preceding 180 days. We also excluded youth taking SGAs via injection (identified by NDC), taking more than one SGA at baseline, or SGA prescriptions indicating 0 day supply dispensed. Youth with a BMI percentile >95% at baseline were excluded to avoid ceiling effects in measuring change in weight z-score.

We also excluded youth with somatic illnesses with the potential to be associated with change in weight.(26-61) These were defined by diagnosis code or use of a medication intended to treat: sickle cell disease, cystic fibrosis, cerebral palsy, cancer, human immunodeficiency virus, Hepatitis B/ C, tuberculosis, liver failure, renal disease, respiratory failure, fatal metabolic disease, aplastic anemia, congenital immune deficiencies, down syndrome, lethal chromosomal abnormalities, Trisomy 13 and 18, autosomal deletion syndrome, serious neuromuscular disorder, polycystic ovarian syndrome, Crohn's Disease and ulcerative colitis, Prader Willi Syndrome and eating disorders. See the protocol posted on the Mini-Sentinel website(62) for a complete list of diagnosis codes and medications employed in this project.

Youth undergoing bariatric surgeries and organ transplant procedures that could affect weight were also excluded. Finally, we excluded pregnant females.

D. MEDICATIONS AND DEFINITION OF EXPOSURE

The primary study medications were aripiprazole, olanzapine, quetiapine, and risperidone. Clozapine, asenapine, lurasidone, iloperidone, paliperidone, and ziprasidone were excluded *a priori* due to low prevalence of utilization in the MSDD population of youth. Olanzapine was also excluded after preliminary analyses because only 201 youth in this population initiated treatment with olanzapine.

Medication exposure was defined by dispensing dates on pharmacy claims data and days supply of medication. Our definition of continuous medication exposure allowed breaks of up to 14 days in availability of the medication (i.e., covered days supply). The index SGA was considered to be discontinued (at the last day of supply) if there was a break in supply of >14 days and youth were censored from the cohort at that time.

E. PRIMARY OUTCOME

The primary outcome was change in sex- and age-adjusted weight z-score(63) between baseline (treatment initiation) and: (i) 12 weeks (+/- 2 weeks), and (ii) 52 weeks (+/- 8 weeks) after treatment initiation. If multiple weight measures were available within either outcome window, the outcome was defined based on the weight measured closest to day 84 or 364, respectively.

F. COVARIATES

We included many covariates in our analyses to increase confounding control. Covariates were grouped into classes and included in models: demographics (age, sex, race, site); mental health diagnoses/medications, women's health conditions, metabolic disorders, respiratory and allergy disorders/medications, gastrointestinal disorders/medications, neurologic and musculoskeletal disorders/medications, antibiotic medication use, other conditions (urinary tract infection, other

infection, malaise/fatigue, hypersomnia, organic sleep disorder, edema, cholecystitis, cholelithiasis, nephrotic syndrome); use of other medications associated with weight gain; and use of other medications associated with weight loss. See Appendix 2 for a complete list of diagnoses, procedures, encounters and medications included in each covariate group. Appendix 3 lists the covariates used in each of the 9 models (7 used for weighting, 2 for outcomes) estimated as part of the study.

The presence or absence of a diagnosis or medication use in a particular class of covariate was coded as a binary variable, with 0 indicating no exposure or the absence of a diagnosis. For example, any concurrent use of stimulant medication was coded as a 0 if no simulant prescriptions were filled and a 1 if at least one stimulant medication was dispensed.

G. STATISTICAL ANALYSES

We calculated descriptive statistics for all dependent and independent variables proposed in the analyses. We evaluated the level and nature of missing data (e.g., physical weight at baseline, 12 weeks and 52 weeks) and produced tables of attrition according to censoring criteria (censoring criteria outlined below). We evaluated the potential for bias associated with differential measurement of height and weight by medication exposure group. Of the initial youth, a high proportion was missing height data, which are needed to calculate BMI z-scores. This led the study team to use weight z-scores instead of BMI z-score as the primary outcome.

H. OUTCOME MODELS

We used ordinary least squares linear regression to model the change in weight z-score separately at (i) 12 weeks (+/- 2 weeks), and (ii) 52 weeks (+/- 8 weeks). A two-sided Wald test, using robust variance estimators (20), was applied to test the significance of the change in weight z-score across the three exposure groups with a 0.05 type I error. We adjusted for baseline covariates in the outcome model and used inverse probability weights (IPW, see below) to control for confounding of SGA selection, missing weight z-scores, and censoring events.

I. INVERSE PROBABILITY WEIGHTING

We used IPWs to balance the medication exposure groups with respect to baseline and time-dependent confounders. All models used stabilized weights. These included confounding by indication, predisposing factors for weight gain, incident events associated with change in weight, informative missing data patterns, and informative censoring and biased outcome (physical weight) measurement. Thus, there were 3 classes of IPW models: missing data, treatment selection, and censoring events (see detailed model descriptions below).

We estimated 7 separate models to generate IPWs: (1) missing weight at baseline, (2) medication choice at baseline, (3) censoring for a weight gain/loss event (e.g., new pregnancy or surgery post-baseline), (4) censoring for medication adding or switching or discontinuation (e.g., adding or switching antipsychotic medications), (5) censoring for disenrollment or death, (6) missing outcome weight measurement at 12 weeks (+/- 2 weeks), and (7) missing outcome weight measurement at 52 weeks (+/- 8 weeks). The rationale for using IPWs to balance for missing physical weights was that youth with non-missing weights are likely different than those with missing physical weights. For example, youth who are overweight at baseline may be preferentially monitored (through weight measurement) because the prescribing physician is more worried about the individual gaining more weight. Similarly, the treatment (medication) selection IPW balances the possibility that youth were prescribed a particular medication due to concerns about an individual's baseline weight. The censoring IPW balances the exposure groups

for time actually exposed to medications. That is, individuals contribute person-time to the outcome model only during the time they are actually exposed to SGA monotherapy. This is often referred to as an analysis of "as treated," "continuous treatment", or "adherence-adjusted treatment" (64-66). The effect estimated is that which would be observed if everyone remained uncensored until the end of follow-up.

IV. IPW MODELS

A. MODEL 1: MISSING BASELING WEIGHT INFORMATION

Rationale: Youth missing baseline physical weight measurements are likely different than youth whose weight was measured.

Outcome: Observation of baseline weight, coded 1 if baseline weight is observed and 0 if the information is missing. We allowed for a window around baseline for weight measurement, which was defined as 90 days prior to SGA initiation and 7 days post initiation.

Model type: Logistic regression.

Analytic sample: Entire cohort (n = 3,722)**.**

Analytic unit: An individual; the dataset to estimate this model had one individual per row.

Covariates: See Appendix 3.

Estimated IPW: The model estimates the probability that baseline weight is observed, adjusting for baseline characteristics. The inverse of this estimated probability is the IPW used to analytically weight the outcome model. If an individual has a high probability of an observed baseline weight, they are analytically down-weighted in the final outcome model. Conversely, if an individual has a low probability of an observed baseline physical weight based on their characteristics, they are analytically up-weighted in the final outcome model.

B. MODEL 2: TREATMENT SELECTION

Rationale: It is likely that clinicians choose SGA medications purposefully at treatment initiation. For example, youth who are overweight at baseline may be less likely to receive prescriptions for medications that have the largest effects on weight gain. This purposeful selection of treatment may subsequently bias the comparison of treatment effects on weight gain.

Outcome: Treatment initiated at baseline (quetiapine, risperidone, or aripiprazole). This is a 3-level categorical outcome variable with risperidone used as the reference medication. Risperidone was chosen for the treatment selection model because it was the largest medication exposure group.

Model type: Multinomial regression.

Analytic sample: Youth in the cohort who have observed baseline weight (n = 1,789). Youth with missing baseline weight (n=1,544) and those with a baseline weight z-score above the 95% percentile (n=389) were excluded leaving a total of 1,789 for the analyses.

Analytic unit: An individual; the dataset used to estimate this model had one individual per row.

Covariates: See Appendix 3.

Estimated IPW: This model estimated the probability of initiating each of the three study treatments (estimated probabilities will sum to 1). The IPW used to analytically weight the outcome model is the inverse of the probability that an individual initiated the observed treatment. For example, if an individual started risperidone at baseline, and the model estimate for the probability of treatment type for this individual were P(quetiapine)=0.22, P(risperidone)=0.60, and P(aripiprazole)=0.18, then the IPW for this individual would be 1/P(risperidone) = 1/(0.60), because risperidone was the treatment he/she was observed to initiate. The same treatment selection analytic weights were used for the 12 week and 52 week outcome analyses.

C. MODELS 3-5: CENSORING DURING FOLLOW-UP

Rationale: Treatment switching and discontinuation are the norm, rather than the exception in antipsychotic medication therapy.(67, 68) Youth who experience milder side effects, such as less weight gain, may be more likely to continue to use the SGA prescribed at baseline. Further, censoring is likely informative insofar as individuals who develop neurologic conditions or metabolic disorders are more likely to switch or discontinue treatment. Patient characteristics and treatment experience may also be related to disenrollment.

Outcome: Binary outcome coded 1 if censored in week 1 to 52 and 0 otherwise. Separate models were fit for each of three different censoring mechanisms:

- **Model 3**: Censored due to treatment changes;
- **Model 4**: Censored due to disenrollment (note, no deaths were observed in our cohort);
- **Model 5**: Censored due to new medical condition (post baseline) related to weight gain.

Model type: Longitudinal logistic regression. Each individual contributes as much time on treatment as is available (until censoring event or end of follow-up at 12 or 52 weeks).

Analytic sample: Youth with observed baseline weight (n = 1,789).

Analytic unit: Person-week; each row in the dataset used to estimate the censoring models represented a person-week pair. Models 3-5 used an identical data structure. The first week included all youth with an observed baseline weight. If the person was censored due to changing treatments in week 1 (or other censoring event), the censorship outcome is 1, otherwise 0 for week one. The long-format dataset contains rows for each individual in each week for as long as he/she remain uncensored. Once the individual was censored, he/she dropped out of the dataset for future weeks. That is, an individual who is observed for all 60 weeks (52 +/- 8 weeks) without a censoring event will be repeated 60 times in the data set with their censorship outcome set to 0 in each of the 60 weeks. An individual who was censored on the 8th week would appear in the data set 8 times; the first 7 times the censorship outcome would be 0 and on the 8th week the outcome would be 1. Covariates were updated if/when new information (e.g., new weight measurements) was observed on individuals. If an individual was censored due to one type of censoring event (e.g., an individual's treatment changes and censoring occurs in model 3) he/she was also removed from the risk set for the other censoring types (models 4 and 5). That is, the first censoring event was used to determine when an individual was censored. As another example, if an individual switches treatment in the 8th week, he/she would have 8 rows of data for all 3 models with the outcome in week 8 being coded 1 in model 3, and 0 in models 4 and 5.

Covariates: See Appendix 3. For models 3-5, covariates were time-varying, defined for each person-week as the value on last day of that week.

Models 3-5 include a covariate for change from baseline in weight z-score, defined based on the weight measure closest in time but prior to the outcome weight measurement window. The rationale for this adjustment is that more rapid weight gain (larger change in weight z-score) is associated with a higher likelihood of weight being measured during the outcome window. When weight has not been measured since baseline, the value of this covariate was set to zero (i.e., there is no known change in weight). The models also include an interaction between change in weight z-score and the number of days prior to the outcome window that this weight was measured. The rationale for this interaction is that changes in weight z-scores measured close to the measurement window are more predictive of weight measurement during the outcome window compared to earlier measures.

Estimated IPW: All three censoring models use an identical approach to construct the censoring weights to be applied to the outcome model. For example, we described the censorship weights for treatment switching. The fitted treatment switching model estimated the probability that an individual was censored due to treatment changes (before week 12 or 52). The probability of continued treatment is 1 minus the probability of being censored. This overall probability of being observed (i.e., not censored) was constructed by multiplying the estimated time-varying probabilities for each individual from week 1 through to the week the outcome weight measurement (12 or 52 weeks). Only uncensored individuals are included in the final outcome model, thus IPW are constructed for individuals with probabilities estimated at all weeks during follow-up. The inverse of this estimated probability (probability of not being censored) is used to analytically weight the final outcome model. If an individual has a high probability of completing follow-up (not censored) they will be analytically down-weighted in the final model, while those individuals who complete follow-up but had a low estimated probability of doing so will be analytically up-weighted in the final analysis.

The estimated probability of completing follow-up at week 12 and 52 for a given censoring mechanism was computed from the same model. The only difference between the IPWs for week 12 and 52 is the number of time-varying probabilities from the propensity models that are multiplied to obtain the final IPW for the outcome model.

D. MODEL 6 AND 7: MISSING OUTCOME OF WEIGHT IN THE 12 & 52 WEEK WINDOWS

Rationale: Youth with high baseline weight or who experience weight gain during follow-up may be more likely to have weight measured at each healthcare visit, and therefore tend to have a non-missing weight during the outcome measurement windows. Further, availability of weight measures in the follow-up period is likely related to making visits for other reasons such as follow-up appointment for chronic medical conditions. IPWs to account for missing outcome information balance the treatment groups with respect to characteristics related to the likelihood of having physical weight outcome measurements. This attenuates bias in observed differences in weight z-score change due to differences in availability of weight measurements (i.e., reduces selection bias due to who has an observed follow-up weight measurement).

Outcome: The outcome is binary and coded 1 if a follow-up physical weight is observed and 0 if missing. The exact outcome window for model 6 was 70-98 days post baseline. The outcome window for model 7 was 308-420 days post baseline.

Model type: Logistic regression.

Analytic sample: Youth in the cohort who have observed baseline weight and who have not been censored prior to the outcome window (12 +/- 2 weeks, 52 +/- 8 weeks). Note that the week-52

outcome cohort and week-12 cohort are not mutually exclusive. That is, youth that remain uncensored by week 45 would be included in both the 12 week and 52 week models.

Analytic unit: An individual; the dataset to estimate this model had one individual per row.

Covariates: See Appendix 3. For models 6 and 7, all covariates were defined as of their value on day 70 and 308 (the first day of each outcome window).

Like Models 3-5, models 6 and 7 include a covariate for change from baseline in weight z-score, defined based on the weight measure closest in time but prior to the outcome weight measurement window. The rationale for this adjustment is that more rapid weight gain (larger change in weight z-score) is associated with a higher likelihood of weight being measured during the outcome window. When weight has not been measured since baseline, the value of this covariate was set to zero (i.e., there is no known change in weight). The models also include an interaction between change in weight z-score and the number of days prior to the outcome window that this weight was measured. The rationale for this interaction is that changes in weight z-scores measured close to the measurement window are more predictive of weight measurement during the outcome window compared to earlier measures.

Estimated IPW: The model estimated the probability that follow-up physical weight is observed, conditional on (i) not being censored and (ii) having a baseline weight. The inverse of this estimated probability is the IPW used to analytically weight the outcome model. Individuals with high probability of an observed follow-up weight were analytically down-weighted in the final model, and those with a low probability were analytically up-weighted.

We fit two different models - one for the 12-week outcome (model 6) and one for the 52-week (model 7) outcome measure.

E. FINAL IPW

Analytic weights from each of the IPW models were stabilized(65, 69) and multiplied to generate a single analytic weight for each individual in the physical weight z-score outcome model. Final IPWs for the 12-week outcome model combined analytic weights from IPW models 1-5 and 6; and final IPWs for the 52-week outcome model combined analytic weights from IPW models 1-5 and 7. Final IPWs were truncated at 10 as per custom.(69) This practice ensures that no individual exerts disproportionate influence in the outcome model.

See the study protocol posted on the Mini-Sentinel website for detailed definitions of the covariates included in all models.(62)

1. Assessing the Adequacy of IPW models

We evaluated the adequacy of the IPW models by visual examination of the analytic weight distributions (graphs) and summarizing estimated weights, including examining extreme weights. We compared the unweighted original cohort (including those without baseline physical weight measurements) and the cohort with observed baseline physical weight analytically weighted to account for this missing information. To assess the treatment selection model (i.e. propensity score), we compared the unweighted and weighted distribution of covariates between those individuals included in the outcome model as well as those in the cohort with baseline physical weight observed to assess the degree of balance achieved.

2. Intent-to-treat Analysis

As per the protocol, we conducted sensitivity analyses using an intent-to-treat approach censoring individuals only for disenrollment (an analytically weighting to account for this censoring). In other words, we allowed for adding medications, switching mediations, discontinuing medications, and other events associated with weight change to assess any differences in outcomes or model interpretation. These ITT analyses were conducted in order to model the effect of initiating antipsychotic treatment on expected weight gain in youth regardless of actual exposure to medications between baseline and 12 or 52 weeks.

V. RESULTS

A. FINAL STUDY POPULATION

The initial MSDD analytic data set included 4,762 individuals aged ≥2 and ≤18 years; 201 were excluded for monotherapy with olanzapine (insufficient power to estimate IPW models); 409 from sites 2 and 3 were excluded for small sample size (and unusual distribution of youth characteristics) and 430 were excluded for other criteria at baseline (pregnancy: n=28, gastrointestinal diagnosis or procedure: n=109, gastrointestinal medications for serious disease: n=2, somatic illnesses: n=2, eating disorder n=4, somatic illness: n=283). Thus, the penultimate analytic database included 3,722 youth meeting inclusion and not meeting exclusion criteria. Of these, 1,544 were missing baseline physical weight measurement leaving 2,178 youth for whom we could calculate change in standardized weight z-score. Another 389 were excluded due to having weight >95th percentile, leaving 1,789 youth meeting all inclusion and not meeting exclusion criteria. Figure 1 presents study cohort development. **Table 1** shows the unweighted distribution of covariates across the medication exposure groups.

Figure 1. Consort Diagram for Sample Development

Key: A – aripriprizole; Q – quetiapine; R – risperidone

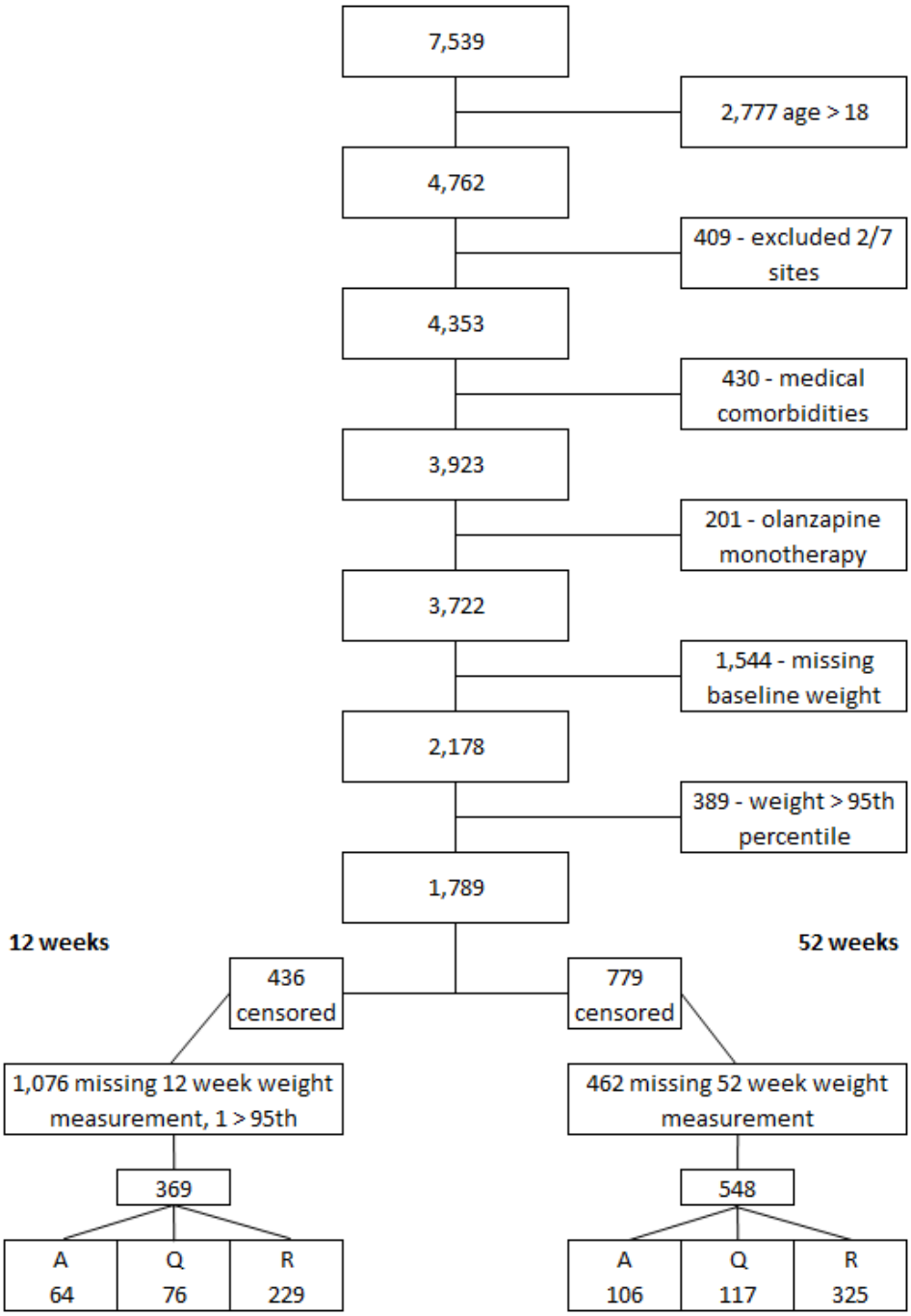

Table 1. Unweighted Distribution of Covariates for Youth with a Baseline Weight Measurement Meeting all Criteria (n = 1,789)

	Unweighted		
	Aripiprazole	**Quetiapine**	**Risperidone**
	N=397	N=360	N=1032
Age, mean	14.3	14.7	11.8
Age ≥ 13	72.8	80.3	44.3
Baseline weight z-score, mean	0.35	0.32	0.09
Male	48.9	47.5	70.3
Race			
White	61.0	59.7	58.7
Am. Indian/Alaska Native	1.5	1.4	1.2
Asian	4.5	4.4	5.6
Black/African American	7.6	5.3	11.1
Hawaiian/PI	1.5	3.6	2.9
Unknown	23.9	25.6	20.5
Site			
1	9.6	24.4	21.5
4	16.9	15.8	21.4
5	6.3	6.9	7.8
6	22.9	23.9	20.8
7	44.3	28.9	28.5
FGA or SGA before washout	3.5	3.9	2.6
Mental Health G1	57.9	50.8	71.0
Mental Health G2	77.3	76.7	58.0
Mental Health G3	25.4	29.4	20.5
Mental Health G4	15.1	23.1	9.3
Mental Health G5	8.8	6.9	18.0
Mental Health G6	57.2	68.1	61.3
Women's Health G2	14.1	13.9	5.2
Women's Health G3	3.8	5.0	1.9
Metabolic encounters G1	54.7	50.8	46.7
GI meds G2	4.8	8.6	4.4
Respiratory encounter G1	24.4	27.2	20.0
Respiratory meds G1	23.2	23.9	22.3
Neuro/Musc encounters G1	6.1	10.3	5.5
Neuro/Musc encounters G2	43.1	51.4	37.7
Neuro/Musc meds G 1	15.4	25.0	14.6
Other Somatic encounters G1	32.2	34.2	32.1
Meds, weight gain	58.4	70.6	44.1
Meds, weight loss	24.9	28.1	44.8
Antibiotics Use	46.6	45.6	43.8

B. INVERSE PROBABILITY WEIGHT MODELS

1. Model 1: Missing Physical Weight Measurement at Baseline

Of the 3,722 youth included, 2,178 (58.5%) had baseline physical weight measurements. **Table 2** shows the results of the logistic regression model predicting the presence (vs. absence) of baseline weight measurement.

Table 2. Logistic Regression Model Predicting Baseline Weight Measurement

Variable	Odds Ratio	Std. Err.	z	P>|z|	95% Conf. Interval	
Age						
<13 years (ref)						
≥13 years	**0.69**	0.06	-4.36	0.000	**0.58**	**0.81**
Sex						
Female (ref)						
Male	0.95	0.08	-0.56	0.572	0.81	1.12
Race						
White (ref)						
Am. Indian/Alaska N						
Asian	0.71	0.21	-1.13	0.258	0.40	1.28
Black/African Am.	1.45	0.31	1.79	0.074	0.96	2.19
Hawaiian/P.I.	**0.76**	0.10	-2.08	0.037	**0.59**	**0.98**
Unknown	1.01	0.26	0.04	0.965	0.61	1.69
Site	0.54	0.05	-7.40	0.000	0.45	0.63
1 (ref)						
4	**1.70**	0.19	4.68	0.000	**1.36**	**2.12**
5	**2.49**	0.47	4.82	0.000	**1.72**	**3.62**
6	**2.06**	0.23	6.54	0.000	**1.66**	**2.56**
7	**3.11**	0.32	10.88	0.000	**2.53**	**3.81**
SGA prior use	0.74	0.14	-1.59	0.113	0.51	1.07
Mental Health G1	1.02	0.09	0.26	0.795	0.86	1.21
Mental Health G2	1.14	0.10	1.53	0.126	0.96	1.34
Mental Health G3	1.14	0.10	1.49	0.137	0.96	1.35
Mental Health G4	0.88	0.10	-1.13	0.257	0.70	1.10
Mental Health G5	0.89	0.09	-1.13	0.258	0.72	1.09
Mental Health G6	1.18	0.09	2.21	0.027	1.02	1.38
Contraceptive Use	**1.41**	0.23	2.14	0.033	**1.03**	**1.93**
Menstruation	1.46	0.36	1.54	0.125	0.90	2.36
Metabolic enc.	**1.53**	0.12	5.52	0.000	**1.31**	**1.77**
GI medication use	0.89	0.16	-0.65	0.516	0.63	1.26
Respiratory enc.	1.07	0.11	0.68	0.496	0.88	1.30
Respiratory meds. use	**1.41**	0.14	3.42	0.001	**1.16**	**1.71**
Neurological enc. 1	1.00	0.16	-0.01	0.992	0.72	1.38
Neurological enc. 2	**1.27**	0.10	3.10	0.002	**1.09**	**1.48**
Neuro. meds. use	**1.51**	0.17	3.61	0.000	**1.21**	**1.90**
Somatic illness	**1.38**	0.12	3.72	0.000	**1.17**	**1.64**
Weight gain meds.	**0.84**	0.07	-2.13	0.033	**0.72**	**0.99**

Variable	Odds Ratio	Std. Err.	z	P>|z|	95% Conf. Interval	
Weight loss meds.	1.02	0.09	0.26	0.797	0.86	1.21
Antibiotics use	**1.49**	0.12	5.02	0.000	**1.28**	**1.74**
constant	0.57	0.08	-3.95	0.000	0.43	0.75

Older age and African-American race were associated more likely to have missing baseline physical weight. Individuals receiving care at sites 4, 5, 6, and 7 were more likely to have baseline physical weight measured than individuals receiving care at site 1. Several of the diagnostic and medication use covariates were significant predictors of baseline weight measurement. Significant predictors of baseline weight being observed included presence of a metabolic disorder (odds ratio (O.R.) = 1.53, 95% confidence interval (C.I. = 1.31 to 1.77), use of respiratory medications (O.R. = 1.41, 95% C.I. = 1.16 to 1.71), neurologic diagnoses (O.R. = 1.27, 95% C.I. = 1.09 to 1.48), use of neurologic medications (O.R. = 1.51, 95% C.I. = 1.21 to 1.90), baseline somatic conditions (O.R. = 1.38, 95% C.I. = 1.17 to 1.64), and baseline use of antibiotics (O.R. = 1.49, 95% C.I. = 1.28 to 1.74).

Table 3 presents the distribution of covariates in the full cohort (n=3,722) and in the subset of individuals with baseline physical weight measurement (n=2,178). The distribution of covariates for those with baseline physical weight measured are presented both unweighted and analytically weighted using the IPW estimated from Model 1. The covariate distribution of the analytically weighted cohort is nearly identical to the full cohort.

Table 3. Balance of Characteristics in the Unweighted and Weighted* populations Compared to the Overall Cohort

Variable	Overall cohort %	Unweighted %	Weighted (unstabilized) %	Weighted (stabilized) %
	N=3722	N=2178	N=2178	N=2178
Numerator variables				
Age, mean	13.2	13.0	13.2	n/a
Age ≥13 years	60.2	59.1	60.1	n/a
Male	62.1	60.1	62.1	n/a
Race				
White	51.9	57.4	52.2	n/a
American Indian/Alaska native	1.4	1.3	1.4	n/a
Asian	4.0	4.8	4.0	n/a
Black/African American	10.7	10.5	10.9	n/a
Hawaiian/Pacific Islander	2.9	3.3	2.9	n/a
Unknown	29.3	22.7	28.6	n/a
Site				
1	26.5	19.7	26.2	n/a
4	17.7	17.7	17.6	n/a
5	6.6	7.7	6.6	n/a
6	23.2	23.3	23.4	
7	26.1	31.5	26.3	
Denominator-Only variables				
BL 1st or 2nd gen antipsychotic use	3.6	3.1	3.7	3.6

Variable	Overall cohort %	Unweighted %	Weighted (unstabilized) %	Weighted (stabilized) %
Mental Health Group 1	62.8	63.3	62.8	62.9
Mental Health Group 2	64.9	67.4	64.8	65.5
Mental Health Group 3	24.3	24.3	24.5	23.2
Mental Health Group 4	12.4	12.6	12.7	12.4
Mental Health Group 5	14.5	13.9	14.5	14.8
Mental Health Group 6	57.5	60.9	58.1	58.7
Women's Health Group 2	7.7	9.2	7.7	8.1
Women's Health Group 3	2.8	3.4	2.9	2.9
Metabolic encounters Group 1	44.4	49.9	44.2	45.6
GI meds Group 2	5.0	5.5	4.9	4.9
Respiratory encounter Group 1	20.3	23.0	20.2	20.4
Respiratory meds Group 1	19.6	23.1	20.0	19.9
Neuro/Musc encounters Group 1	5.8	6.5	5.7	5.9
Neuro/Musc encounters Group 2	38.8	42.4	38.9	38.9
Neuro/Musc meds Group 1	14.9	17.5	14.8	14.5
Other Somatic encounters Group 1	27.7	32.2	27.7	28.1
Other meds assoc w/ weight gain	52.8	53.3	53.0	53.3
Other meds assoc w/ weight loss	35.1	35.5	35.5	35.3
Antibiotics	39.7	45.6	39.6	40.2

* Among those with a baseline weight measure

2. Model 2: Treatment Assignment

The treatment assignment model estimated the probability of initiating each of the 3 study treatments (estimated probabilities sum to 1). Of the 2,178 youth with baseline weight measurement, 389 (17.8%) were excluded due to baseline weight >95th percentile leaving 1,789 in analytic sample. Of these, 397 (22.2%) were prescribed aripiprazole, 360 (20.1%) quetiapine, and 1,032 (57.7%) risperidone.

Table 12 (see Appendix 2) presents the results of the multinomial regression model with risperidone as the reference category. Age, sex, African-American race and health care site were significant demographic predictors of being prescribed aripiprazole or quetiapine relative to risperidone. Significant predictors of youth being prescribed aripiprazole or quetiapine relative to risperidone were: mental health conditions (Group 2 - depression, Group 6 - other), metabolic conditions, other medications associated with weight gain or loss, and baseline physical weight z-score.

Table 13 (See Appendix 2) presents the distribution of covariates across the treatment groups in the unweighted and weighted cohorts. The shaded cells highlight that the model achieves good balance across the medication exposure groups with respect to known confounders included in the model.

3. Model 3: Censoring Due to Treatment Switching

Model 3 estimated the probability that an individual was censored due to treatment changes before the outcome physical weight measure at 12 or 52 weeks.

Table 4. Treatment Switching Censoring Model

Variable	O.R.	Std. Err.	z	P>|z|	95% Conf. Interval	
Medication Group						
Aripiprazole (ref)	1					
Quetiapine	0.79	0.14	-1.34	0.181	0.57	1.11
Risperidone	0.89	0.13	-0.81	0.420	0.67	1.18
Age						
<13 years (ref)	1					
≥13 years	0.90	0.13	-0.75	0.450	0.68	1.19
Sex						
Female (ref)	1					
Male	1.06	0.15	0.40	0.691	0.80	1.39
Race						
White (ref)	1					
Am. Indian/Alaska Nat.	1.01	0.43	0.03	0.975	0.44	2.32
Asian	1.36	0.35	1.19	0.233	0.82	2.25
Black/African American	1.19	0.25	0.83	0.408	0.79	1.80
Hawaiian/PI	0.84	0.37	-0.39	0.696	0.36	1.98
Unknown	0.86	0.14	-0.98	0.327	0.63	1.17
Site						
1 (ref)	1					
4	0.82	0.15	-1.12	0.264	0.57	1.16
5	0.75	0.21	-1.01	0.313	0.43	1.31
6	0.78	0.14	-1.35	0.178	0.55	1.12
7	0.93	0.15	-0.45	0.656	0.68	1.28
Weight measures						
Baseline weight z-score, spline[a] 1	1.12	0.19	0.71	0.480	0.81	1.56
Baseline weight z-score, spline[a] 2	0.87	0.16	-0.76	0.445	0.61	1.24
Change in weight z-score, spline[b] 1	1.06	0.67	0.09	0.927	0.31	3.63
Change in weight z-score, spline[b] 2	2.93	1.65	1.92	0.055	0.98	8.81
Interactions [c]						
change spline 1*(1-2 months)	1.27	1.16	0.26	0.792	0.21	7.64
change spline 1*(2-3 months)	0.50	0.33	-1.04	0.297	0.14	1.84
change spline 1*(>3 months)	1.44	1.14	0.46	0.645	0.31	6.76
change spline 2*(1-2 months)	0.24	0.22	-1.57	0.115	0.04	1.42
change spline 2*(2-3 months)	1.64	1.12	0.73	0.465	0.43	6.25
change spline 2*(>3 months)	0.31	0.27	-1.34	0.179	0.06	1.72
Follow-up time specifications						
Time in weeks, spline[d] 1	**0.95**	0.01	-6.52	0.000	**0.93**	**0.96**
Time in weeks, spline[d] 2	**1.02**	0.01	2.06	0.040	**1.00**	**1.04**
Covariates						
GI encounter	1.78	0.71	1.45	0.148	0.82	3.88
Endpoint illness	**1.90**	0.42	2.87	0.004	**1.22**	**2.94**
Somatic excl.	1.25	0.46	0.60	0.550	0.60	2.58
Eating Disorder	2.41	1.28	1.65	0.098	0.85	6.81

Variable	O.R.	Std. Err.	z	P>|z|	95% Conf. Interval	
Prior Use	0.69	0.27	-0.95	0.344	0.32	1.49
MH Group 1	0.88	0.13	-0.81	0.420	0.66	1.19
MH Group 2	1.11	0.16	0.69	0.493	0.83	1.48
MH Group 3	**2.23**	0.28	6.40	0.000	**1.74**	**2.84**
MH Group 4	**1.41**	0.22	2.28	0.022	**1.05**	**1.91**
MH Group 5	0.98	0.17	-0.10	0.919	0.70	1.37
MH Group 6	**1.40**	0.20	2.34	0.019	**1.06**	**1.86**
Contraceptive use	1.06	0.22	0.28	0.782	0.70	1.60
Women's Health	1.37	0.37	1.16	0.245	0.80	2.34
Metabolic Enc.	1.29	0.17	1.95	0.051	1.00	1.66
GI Meds Use	0.96	0.20	-0.21	0.834	0.64	1.44
Resp. Enc.	0.99	0.13	-0.10	0.919	0.76	1.28
Resp. Meds.	1.13	0.15	0.97	0.333	0.88	1.46
Neurologic Enc. 1	1.12	0.21	0.58	0.562	0.77	1.61
Neurologic Enc. 2	1.15	0.14	1.21	0.228	0.92	1.45
Neurologic meds.	0.86	0.13	-0.98	0.328	0.64	1.16
Somatic illness meds.	1.06	0.13	0.51	0.612	0.84	1.36
Weight gain meds.	**1.36**	0.18	2.37	0.018	**1.05**	**1.75**
Weight loss meds.	1.10	0.16	0.64	0.523	0.83	1.45
Antibiotic use	**1.26**	0.15	1.92	0.055	**1.00**	**1.59**
Constant	0.00	0.00	-15.67	0.000	0.00	0.01

[a] Baseline weight z-score entered as a cubic spline with knots at -1, 0, and 1

[b] Change in weight z-score entered as a cubic spline with knots at 0, 0.25, and 0.50.

[c] Interactions between change in weight z-score (spline), and indicators for time since weight score was measured (<1 month, 1-2 months, 2-3 months, and >3 months).

[d] Follow-up time entered as a cubic spline with knots at 12, 24, and 36 weeks.

Table 4 presents the results of the treatment switching model. Youth initiating treatment with quetiapine and risperidone were no more likely to switch treatment than youth initiating treatment with aripiprazole. Neither demographic characteristics nor site were statistically significant predictors of treatment switching. Baseline weight z-score and change in weight z-score (between baseline and time t) also were not significant predictors of censoring due to treatment switching. Follow-up time, measured as weeks from baseline and entered in the model as a cubic spline with knots at 12, 24, and 36-weeks, was significantly associated with censoring due to treatment switching.

There were 7 significant clinical variables associated with treatment switching: endpoint illness diagnosis (O.R. = 1.90, 95% C.I. = 1.22 to 2.94), metabolic disorder encounters (O.R. = 1.29, 95% C.I. = 1.0 to 1.66), group 3 mental health disorders (O.R. = 2.23, 95% C.I. = 1.74 to 2.84), group 4 mental health disorders (O.R. = 1.41, 95% C.I. = 1.05 to 1.91), group 6 mental health disorders (O.R. = 1.40, 95% C.I. = 1.06 to 1.86), medications associated with weight gain (O.R. = 1.36, 95% C.I. = 1.05 to 1.75), and antibiotic use (O.R. = 1.26, 95% C.I. = 1.0 to 1.59) were all significant predictors.

4. Model 4: Censoring due to Disenrollment

Table 5 presents the results of the model predicting disenrollment (there were no observed deaths). Only race/ethnicity was a significant predictor with American-Indian and Alaska Native youth being

more likely to disenroll (O.R. = 2.75, 95% C.I. = 1.16 to 6.71) as well as youth with unknown race/ethnicity (O.R. = 2.81, 95% C.I. = 2.03 to 3.88).

Table 5. Model of Censoring Due to Disenrollment or Death

Variable	O.R.	Std. Err.	z	P>|z|	95% Conf. Int.	
Medication						
Aripiprazole (ref)	1					
Quetiapine	0.96	0.22	-0.18	0.860	0.61	1.52
Risperidone	0.98	0.19	-0.11	0.914	0.67	1.43
Age						
<13 years (ref)	1					
≥13 years	0.84	0.13	-1.08	0.278	0.62	1.15
Sex						
Female (ref)	1					
Male	1.29	0.21	1.56	0.118	0.94	1.79
Race						
White (ref)	1					
Am. Indian/Alas..	2.75	1.21	2.29	0.022	1.16	6.51
Asian	0.39	0.25	-1.47	0.142	0.11	1.37
Black/African A..	0.84	0.29	-0.51	0.612	0.43	1.65
Hawaiian/PI	1.34	0.74	0.53	0.593	0.46	3.94
Unknown	2.81	0.46	6.28	0.000	2.03	3.88
Site						
1 (ref)	1					
4	0.99	0.22	-0.04	0.968	0.64	1.54
5	1.01	0.39	0.02	0.983	0.47	2.16
6	0.58	0.14	-2.30	0.021	0.37	0.92
7	0.84	0.18	-0.84	0.403	0.56	1.26
Weight loss medication	0.90	0.14	-0.68	0.495	0.66	1.23
Weight measures						
Baseline weight z-score, spline[a] 1	1.03	0.17	0.17	0.866	0.75	1.41
Baseline weight z-score, spline[a] 2	1.12	0.22	0.57	0.570	0.76	1.66
Follow-up time specifications						
Time in weeks, spline[b] 1	1.02	0.01	1.27	0.204	0.99	1.04
Time in weeks, spline[b] 2	0.98	0.01	-1.37	0.171	0.96	1.01
Constant	0.00	0.00	-18.57	0.000	0.00	0.00

[a] Baseline weight z-score entered as a cubic spline with knots at -1, 0, and 1

[b] Follow-up time entered as a cubic spline with knots at 12, 24, and 36 weeks.

5. Model 5: Censoring Due to New Diagnoses or Medication Use (post baseline)

Table 6 shows the results of the censoring model predicting the occurrence of incident medical diagnoses (e.g., cancer diagnosed after baseline) or incident use of medications associated with weight gain after baseline.

Table 6. Censoring Model for Incident Medical Condition or Weight Gain Medication Use

Variable	O.R.	Std. Err.	z	P>|z|	95% Conf. Int.	
Medication						
Aripiprazole	1					
Quetiapine	**0.57**	0.12	-2.68	0.007	**0.37**	**0.86**
Risperidone	1.00	0.16	-0.01	0.991	0.73	1.36
Age						
<13 years (ref)	1					
≥13 years	1.28	0.18	1.73	0.083	0.97	1.68
Sex						
Female (ref)	1					
Male	0.77	0.11	-1.82	0.068	0.59	1.02
Race						
White	1					
Am. Indian/Alaska Nat.	2.20	0.93	1.87	0.062	0.96	5.01
Asian	0.48	0.20	-1.76	0.079	0.21	1.09
Black/African American	0.77	0.21	-0.97	0.331	0.45	1.31
Hawaiian/PI	1.08	0.45	0.19	0.846	0.48	2.43
Unknown	1.11	0.18	0.67	0.502	0.81	1.53
Site						
1 (ref)						
4	0.97	0.20	-0.16	0.871	0.64	1.46
5	1.13	0.36	0.39	0.696	0.60	2.13
6	0.89	0.19	-0.55	0.583	0.58	1.35
7	0.92	0.18	-0.41	0.682	0.64	1.34
Weight measures						
Baseline weight z-score, spline[a] 1	0.85	0.14	-1.02	0.306	0.62	1.16
Baseline weight z-score, spline[a] 2	1.32	0.25	1.48	0.139	0.91	1.91
Change in weight z-score, spline[b] 1	1.57	1.79	0.40	0.691	0.17	14.64
Change in weight z-score, spline[b] 2	1.64	1.60	0.51	0.610	0.24	11.11
Interactions [c]						
change spline 1*(1-2 months)	0.81	0.96	-0.18	0.859	0.08	8.18
change spline 1*(2-3 months)	0.19	0.28	-1.14	0.254	0.01	3.25
Follow-up time specifications						
Time in weeks, spline[d] 1	**0.95**	0.01	-4.63	0.000	**0.93**	**0.97**
Time in weeks, spline[d] 2	**1.03**	0.01	2.97	0.003	**1.01**	**1.06**
Weight loss meds. Use	**0.64**	0.10	-2.86	0.004	**0.47**	**0.87**
Metabolic disorder enc.	0.80	0.11	-1.64	0.101	0.62	1.04
Constant	0.01	0.00	-16.61	0.000	0.00	0.01

[a] Baseline weight z-score entered as a cubic spline with knots at -1, 0, and 1

[b] Change in weight z-score entered as a cubic spline with knots at 0, 0.25, and 0.50.

[c] Interactions between change in weight z-score (spline), and indicators for time since weight score was measured (<1 month, ≥1 month).

[d] Follow-up time entered as a cubic spline with knots at 12, 24, and 36 weeks.

Youth initiating treatment with quetiapine were less likely to be censored for an incident medical condition or treatment/medication use (O.R. = 0.57, 95% C.I. = 0.37 to 0.86). Incident use of medications

associated with weight loss (e.g., stimulants) was associated with a lower likelihood of censoring (O.R. = 0.64, 95% C.I. = 0.47 to 0.87). Follow-up time spline specifications (weeks from baseline) was significantly associated with censoring (spline 1 O.R. = 0.95, 95% C.I. = 0.93 to 0.97; spline 2 O.R. = 1.03, 95% C.I. 1.01 to 1.06).

6. Model 6: Presence of Follow-up Weight Measurement at 12 +/- 2 Weeks

Of the 1,789 youth with baseline weight measurement and weight <95th percentile, 1,446 (80.8%) remained uncensored during the 12 week outcome measurement window (i.e., by the end of week 14 there were 343 youth censored). Only 370 of 1,446 (25.6%) had physical weight measurements after baseline and during the 12 week outcome window. **Table 14** (see Appendix 2) presents the results of the logistic regression model predicting the measurement of physical weight at 12 weeks. Youth initiating treatment with risperidone were more likely to have outcome weight measurements compared to youth initiating treatment with aripiprazole (O.R. = 1.50, 95% C.I. = 1.06 to 2.12). Individuals taking medications to treat respiratory conditions were also more likely to have non-missing weight measurement at 12 weeks (O.R. = 1.41, 95% C.I. = 1.04 to 1.89). Baseline weight z-score, entered as cubic splines with knots at -1, 0, and 1, was a significant predictor of having a follow-up weight measurement within the 12-week outcome window.

Table 15 (see Appendix 2) shows the distribution of covariates across the overall cohort who were not censored by the end of follow-up at 12-weeks, and the 370 youth whose weight was measured during the 12-weeks follow-up window. Both unweighted and weighted distributions are shown for those with outcome measures. Comparison of the overall cohort (n=1,446) and the analytically weighted cohort of 370 youth with physical weight measurements demonstrates good balance was achieved via the IPW calculated.

7. Model 7: Follow-up Weight Measurement at 52 +/- 8 Weeks

Of the 1,789 youth, there were 1,010 (56.5%) not censored by the end of the 52-week follow-up window and were included in the model predicting non-missing weight at 52 weeks. Of the 1,010 youth, 548 (54.3%) had physical weight measured during the 52 week outcome window.

Table 7 shows the results of the logistic regression model predicting non-missing physical weight measured at 52 weeks.

Table 7. Model Predicting Measurement of Weight at 52 weeks, +/- 8 weeks

Variable	O.R.	Std. Err.	z	P>|z|	95% Conf. Int.	
Medication						
Aripiprazole (ref)	1					
Quetiapine	1.17	0.25	0.71	0.475	0.76	1.79
Risperidone	1.10	0.21	0.50	0.615	0.76	1.59
Age						
<13 years (ref)	1					
≥13 years	**0.63**	0.11	-2.68	0.007	**0.44**	**0.88**
Sex						
Female (ref)	1					
Male	**0.70**	0.12	-2.08	0.038	**0.50**	**0.98**
Race						

Variable	O.R.	Std. Err.	z	P>|z|	95% Conf. Int.	
White (ref)	1					
Am. Indian/Alaska Nat.	0.25	0.23	-1.51	0.132	0.04	1.52
Asian	1.30	0.45	0.76	0.450	0.66	2.56
Black/African American	1.11	0.28	0.40	0.690	0.67	1.81
Hawaiian/PI	0.62	0.29	-1.04	0.298	0.25	1.54
Unknown	**0.66**	0.12	-2.26	0.024	**0.46**	**0.95**
Site						
1 (ref)						
4	0.83	0.20	-0.78	0.434	0.52	1.32
5	1.80	0.64	1.66	0.098	0.90	3.60
6	1.41	0.33	1.47	0.142	0.89	2.21
7	1.06	0.23	0.27	0.786	0.70	1.62
Weight measures						
Baseline weight z-score, spline[a] 1	0.86	0.14	-0.91	0.363	0.63	1.18
Baseline weight z-score, spline[a] 2	1.09	0.21	0.42	0.674	0.74	1.59
Change in weight z-score, spline[b] 1	0.57	0.34	-0.95	0.343	0.18	1.83
Change in weight z-score, spline[b] 2	3.27	2.28	1.70	0.090	0.83	12.81
Interactions [c]						
change spline 1*(1-2 months)	1.91	2.17	0.57	0.567	0.21	17.69
change spline 1*(2-3 months)	1.13	1.20	0.11	0.911	0.14	9.04
change spline 1*(>3 months)	4.38	3.38	1.91	0.056	0.96	19.92
change spline 2*(1-2 months)	0.26	0.30	-1.15	0.250	0.03	2.59
change spline 2*(2-3 months)	2.14	2.86	0.57	0.571	0.15	29.45
change spline 2*(>3 months)	0.09	0.08	-2.73	0.006	0.02	0.51
Incident Diagnoses and Util.						
GI encounters	0.84	0.46	-0.31	0.754	0.29	2.45
endpoint illness	0.84	0.24	-0.64	0.524	0.48	1.45
somatic illness excl.	0.70	0.35	-0.70	0.481	0.26	1.88
Eating Disorder	0.64	0.65	-0.43	0.665	0.09	4.70
SGA Prior Use	0.64	0.23	-1.22	0.221	0.31	1.31
Mental Health Group 1	1.02	0.19	0.08	0.934	0.71	1.46
Mental Health Group 2	0.87	0.15	-0.85	0.396	0.62	1.21
Mental Health Group 3	0.90	0.16	-0.61	0.542	0.64	1.26
Mental Health Group 4	0.67	0.14	-1.87	0.061	0.43	1.02
Mental Health Group 5	**0.68**	0.13	-2.01	0.044	**0.47**	**0.99**
Mental Health Group 6	1.02	0.17	0.13	0.899	0.74	1.40
Contraceptives Use	**1.84**	0.53	2.12	0.034	**1.05**	**3.23**
Menstruation	1.24	0.51	0.52	0.600	0.55	2.77
Metabolic Enc.	1.12	0.17	0.75	0.456	0.83	1.52
GI medication use	1.03	0.30	0.10	0.917	0.58	1.82
Respiratory enc.	0.84	0.14	-1.04	0.296	0.61	1.17
Respiratory meds.	1.37	0.23	1.90	0.057	0.99	1.90
Neurological enc. 1	**2.08**	0.55	2.79	0.005	**1.24**	**3.49**
Neurological enc. 2	0.95	0.14	-0.33	0.744	0.72	1.27
Neurologic meds. Use	1.24	0.23	1.17	0.241	0.87	1.78

Variable	O.R.	Std. Err.	z	P>|z|	95% Conf. Int.	
Somatic illness	1.22	0.18	1.35	0.178	0.91	1.63
Weight gain meds. Use	1.08	0.17	0.50	0.614	0.79	1.48
Weight loss meds. Use	1.26	0.21	1.37	0.171	0.91	1.75
Antibiotics Use	**1.49**	0.22	2.67	0.008	**1.11**	**1.99**
Constant	0.99	0.38	-0.01	0.988	0.47	2.12

[a] Baseline weight z-score entered as a cubic spline with knots at -1, 0, and 1

[b] Change in weight z-score entered as a cubic spline with knots at 0, 0.25, and 0.50.

[c] Interactions between change in weight z-score (spline), and indicators for time since weight score was measured (<1 month, 1-2 months, 2-3 months, and >3 months).

Youth aged ≥13 years (compared to those aged < 13 years) was had lower likelihood of observed physical weight at 52 weeks (O.R. = 0.63, 95% C.I. = 0.44 to 0.88). Sex was also significant with males being less likely than females to have physical weight measured (O.R. = 0.70, 95% C.I. = 0.50 to 0.98). Individuals with unknown race were also less likely to have weight measured (O.R. = 0.66, 95% C.I. = 0.46 to 0.95).

Several diagnosis and utilization factors significantly increased the odds of weight being measured including the mental health diagnoses included in Group 5 (O.R. = 0.68, 95% C.I. = 0.47 to 0.99), neurologic disorder encounters (O.R. = 2.08, 95% C.I. = 1.24 to 3.49), contraceptive use (O.R. = 1.84, 95% C.I. = 1.05 to 3.23), and antibiotics use (O.R. = 1.49, 95% C.I. = 1.11 to 1.99). Baseline weight z-score and change in weight z-score prior to the outcome window were not related to the likelihood of having a measurement within the window.

Table 16 (see Appendix 2) shows the distribution of covariates across the cohort who were not censored prior to 60-weeks (n=1,010), and the 548 youth whose physical weight was measured at 52 weeks in the cohorts. We present the covariate distribution, both weighted and unweighted in the 548 youth with the 52 week outcome observed. Comparison of the overall cohort (n=1,010) and analytically weighted cohort of 548 youth with physical weight measurements demonstrates good balance was achieved via the IPW calculated.

C. FINAL ANALYTIC WEIGHTS

Analytic weights from each of the 7 IPW models were multiplied and truncated if appropriate. Only 12 individuals had a final combined analytic weight greater than 10, prior to truncation. **Table 8** shows the distribution of covariates across the overall cohort as well as the unweighted and weighted distribution of covariates in the analytic sample for the 12 and 52 week outcome analysis. In general, the final IPWs balanced the three treatment groups in the analytic sample and in the full cohort with respect to known confounders.

Table 8. Distribution of Covariates for the Overall, 12 and 52 Week Youth Populations

Variable	Overall cohort %	12-week outcome		52-week outcome	
		Unweighted %	Weighted %	Unweighted %	Weighted %
	n=3,722	n=369	n=369	n=548	n=548
Age, mean	13.2	12.8	12.7	12.6	12.6
Age ≥13 years	60.2	53.9	54.7	51.8	49.0
Male	62.1	61.8	61.7	57.7	59.4
Race					
White	51.9	62.1	60.9	61.1	59.5
American Indian/Alaska native	1.4	2.2	1.7	0.4	0.3
Asian	4.0	7.6	8.3	6.8	5.5
Black/African American	10.7	8.7	8.6	11.9	11.0
Hawaiian/Pacific Islander	2.9	3.0	2.7	2.7	3.4
Unknown	29.3	16.5	17.8	17.2	20.3
Site					
1	26.5	19.0	20.4	17.2	17.3
4	17.7	17.1	16.7	16.8	17.2
5	6.6	7.1	7.2	9.1	9.5
6	23.2	21.7	21.7	26.5	25.5
7	26.1	35.2	34.0	30.5	30.5
Denominator-Only variables					
BL 1st or 2nd gen antipsychotic use	3.6	2.2	4.3	2.9	4.0
Mental Health Group 1	62.8	66.1	64.6	67.0	63.6
Mental Health Group 2	64.9	68.0	62.3	62.4	59.6
Mental Health Group 3	24.3	17.6	20.2	17.0	19.8
Mental Health Group 4	12.4	11.9	12.7	9.1	8.9
Mental Health Group 5	14.5	16.0	15.0	14.1	18.3
Mental Health Group 6	57.5	65.6	59.8	62.6	59.8
Women's Health Group 2	7.7	10.0	7.3	8.4	7.4
Women's Health Group 3	2.8	1.9	1.4	2.0	1.8
Metabolic Encounters Group 1	44.4	48.5	41.9	50.0	44.0
GI meds Group 2	5.0	6.0	5.0	5.1	4.6
Respiratory encounter Group 1	20.3	26.0	19.9	23.2	20.2
Respiratory meds Group 1	19.6	28.2	21.6	24.8	20.2
Neuro/Musc encounters Group 1	5.8	7.6	5.7	8.2	5.8
Neuro/Musc encounters Group 2	38.8	45.0	37.2	39.6	35.0
Neuro/Musc meds Group 1	14.9	19.5	15.2	17.2	11.9
Other Somatic encounters Group 1	27.7	32.5	28.1	34.3	27.6
Other meds assoc w/ weight gain	52.8	59.1	54.6	58.6	58.1
Other meds assoc w/ weight loss	35.1	38.5	38.2	41.8	37.4
Antibiotics Use	39.7	47.4	38.8	45.8	37.3

D. OUTCOME MODELS: WEIGHT CHANGE AT 12 +/- 2 WEEKS AND 52 +/- 8 WEEKS FROM BASELINE

Results of the analytically weighted ordinary least squares linear regression models predicting change in physical weight z-score at 12 and 52 weeks are detailed in **Table 9** and **Table 10**, respectively. The coefficients of these models represent expected change in physical weight z-score. At 12 weeks, there was not a statistically significant difference in expected change in physical weight between the medications after controlling for age, sex, race, and site. At 52 weeks; however, the expected change in physical weight z-score was lower for quetiapine compared to aripiprazole (O.R. = -0.24, 95% C.I. = -0.44 to -0.03).

Table 9. Results of the 12 Week Weight Gain Model (n = 369)

Variable	Coeff.	Std. Err.	z	P>|z|	95% Conf. Int.	
Study drug						
Aripiprazole	1					
Quetiapine	-0.10	0.07	-1.52	0.130	-0.24	0.03
Risperidone	0.00	0.05	-0.09	0.928	-0.11	0.10
Age (years)						
Age <13 years	1					
Age ≥13 years	-0.03	0.04	-0.79	0.432	-0.11	0.05
Sex						
Female	1					
Male	**0.14**	0.04	3.16	0.002	**0.05**	**0.22**
Race						
White (ref)	1					
American Indian/Alaska Nat.	0.10	0.08	1.26	0.210	-0.06	0.26
Asian	**-0.15**	0.07	-2.03	0.043	**-0.29**	**0.00**
Black/African American	0.03	0.07	0.43	0.670	-0.10	0.16
Hawaiian/Pacific Islander	-0.01	0.08	-0.07	0.947	-0.17	0.16
Unknown	-0.02	0.06	-0.26	0.798	-0.14	0.11
Site						
1 (ref)	1					
4	-0.08	0.06	-1.37	0.171	-0.20	0.04
5	-0.03	0.07	-0.44	0.660	-0.17	0.11
6	0.00	0.00	0.23	0.814	0.00	0.00
7	0.00	0.00	-0.09	0.932	0.00	0.00
Weight Measures						
Baseline weight z-score, spline[a] 1	-0.08	0.06	-1.37	0.171	-0.20	0.04
Baseline weight z-score, spline[a] 2	-0.03	0.07	-0.44	0.660	-0.17	0.11
Time Measures						
Time between index and BL weight measure	0.00	0.00	0.23	0.814	0.00	0.00
Time between index and 12 week weight measure	0.00	0.00	-0.09	0.932	0.00	0.00
Constant	0.24	0.22	1.06	0.289	-0.20	0.68

[a] Baseline weight z-score entered as a cubic spline with knots at -1, 0, and 1

Table 10. Results of the 52 Week Weight Gain Model (n = 548)

Variable	Coeff.	Std. Err.	z	P>|z|	95% Conf. Int.	
Study drug						
Aripiprazole (ref)	1					
Quetiapine	**-0.24**	0.10	-2.30	0.022	**-0.44**	**-0.03**
Risperidone	-0.01	0.09	-0.14	0.885	-0.20	0.17
Age						
< 13	1					
≥ 13	-0.03	0.05	-0.56	0.579	-0.13	0.07
Sex						
Female (ref)	1					
Male	-0.05	0.06	-0.85	0.396	-0.16	0.06
Race						
White (ref)	1					
American Indian/Alaska Nat.	-0.23	0.34	-0.69	0.493	-0.91	0.44
Asian	**-0.22**	0.08	-2.61	0.009	**-0.39**	**-0.05**
Black/African American	**-0.27**	0.09	-3.10	0.002	**-0.44**	**-0.10**
Hawaiian/Pacific Islander	0.16	0.13	1.24	0.216	-0.09	0.40
Unknown	0.00	0.07	-0.07	0.948	-0.14	0.13
Site						
1 (ref)	1					
4	-0.03	0.07	-0.43	0.665	-0.17	0.11
5	**-0.21**	0.09	-2.23	0.026	**-0.39**	**-0.03**
6	-0.03	0.07	-0.45	0.654	-0.18	0.11
7	-0.02	0.07	-0.28	0.779	-0.15	0.12
Weight Measures						
Baseline weight z-score, spline[a] 1	**-0.20**	0.05	-4.34	0.000	**-0.29**	**-0.11**
Baseline weight z-score, spline[a] 2	0.09	0.06	1.54	0.123	-0.02	0.20
Time Measures						
Time between index and BL weight measure	0.00	0.00	0.37	0.713	0.00	0.00
Time between index and 12 week weight measure	0.00	0.00	0.73	0.465	0.00	0.00
Constant	0.14	0.45	0.30	0.765	-0.75	1.02

[a] Baseline weight z-score entered as a cubic spline with knots at -1, 0, and 1

For easier interpretation, estimated mean changes in physical weight z-score at 12 and 52 weeks are shown in **Table 11**. These results show the estimated change in z-score by medication group to aid in ease of interpretation. The estimated group means presented from the primary analytic model represent the expected weight z-score change for a white male, aged <13 years, receiving care at site 7 who had a baseline weight z-score of zero (i.e. is at the median of the age-adjusted weight curve).

Average change in physical weight z-score was greater than that expected due to normal growth in every medication/follow-up group with the exception of quetiapine at 52 weeks. For example, adjusted for normal growth, youth initiating treatment with aripiprazole had an increase of 0.33 standard deviations (95% C.I. = 0.18 to 0.48) at 12 weeks and 0.37 standard deviations (95% C.I. = 0.23 to 0.50) at 52 weeks in the main analysis. Youth initiating treatment with risperidone experienced similar changes

in adjusted weight z-score with a gain of 0.32 (95% C.I. = 0.21 to 0.44) at 12 weeks and 0.35 (95% C.I. = 0.23 to 0.48) at 52 weeks. The change in weight z-score for quetiapine was 0.22 (95% C.I. = 0.08 to 0.37) at 12 weeks and 0.13 (95% C.I. = -0.01 to 0.27) at 52 weeks. The results of the intent-to-treat (ITT) analysis are also shown in **Table 11**. The ITT analyses (where the only censoring event was disenrollment) produced largely similar results.

Table 11. Mean Change in Weight z-score Between Baseline and Endpoints

	Change from baseline, weight z-score		
	Aripiprazole	Quetiapine	Risperidone
	mean (95% CI)	mean (95% CI)	mean (95% CI)
Outcome: 12-weeks			
Treatment as delivered	**0.33 (0.18, 0.48)**	**0.22 (0.08, 0.37)**	**0.32 (0.21, 0.44)**
Intent to treat analysis	**0.28 (0.16, 0.40)**	**0.19 (0.07, 0.31)**	**0.28 (0.19, 0.38)**
Outcome: 52-weeks			
Treatment as delivered	**0.37 (0.11, 0.63)**	0.13 (-0.01, 0.27)	**0.35 (0.23, 0.48)**
Intent to treat analysis	**0.37 (0.23, 0.50)**	**0.20 (0.07, 0.34)**	**0.41 (0.30, 0.51)**

***** Estimated group means from the main effects model, assuming covariate values: male, age<13, site=7, race=white, and a baseline z-score=0.

Table 19 (see Appendix 2) shows the estimated adjusted mean difference between medication exposure groups for the change in weight z-score. The relative change in weight z-score for all pairwise comparisons is shown for the overall model and stratified by age, sex, and baseline weight subgroups at 12 and 52 weeks.

Overall, there was no difference in adjusted weight z-score change between the medications at week 12. However, at week 52, compared to youth taking aripiprazole, youth taking quetiapine (β = -0.24, 95% C.I. = -0.44 to -0.03) and risperidone (β = -0.22, 95% C.I. = -0.33 to -0.04) had lower adjusted change in weight z-score.

Adjusted mean differences between the treatment groups varied by some age, sex, and baseline physical weight subgroups. At 12 weeks, males taking quetiapine had less weight gain compared to males taking aripiprazole or risperidone. However, the same comparisons were not significantly different for females. Also, at 52 weeks, youth who were overweight at baseline and taking quetiapine compared to risperidone had slightly less physical weight gain than youth who were underweight or normal weight at baseline.

Table 20 (see Appendix 2) shows estimated mean change in physical weight z-score for a range of baseline z-score values from the sex subgroup model. In general, increases in weight over-and-above those expected due to normal growth were largest for youth with the lowest baseline weights (e.g., note the difference in mean weight z-scores for youth with baseline weight z-scores of -1.0 with those beginning treatment with a baseline weight z-scored of 1.0). At 12 weeks, males taking aripiprazole or risperidone tended to gain more physical weight than females for comparable baseline physical weights; weight gain was comparable at 12 weeks among males and females taking quetiapine. At 12 weeks the largest difference is between males taking; specifically males with a baseline weight z-score of zero and using quetiapine gained 0.16 standard deviations (95% C.I. = 0.0 to 0.32) whereas individuals using aripiprazole gained 0.37 (95% C.I. = 0.20 to 0.54) and males taking risperidone gained 0.33 (95% C.I. = 0.22 to 0.44).

At 52 weeks, female weight gain in females was similar to males for those taking quetiapine or risperidone, but greater than weight gain experienced by males taking aripiprazole. For example, females taking aripiprazole with a baseline physical weight z-score of zero had larger adjusted weight gain (0.50, 95% C.I. = 0.17 to 0.84) than comparable males (0.23, 95% C.I. = -0.06 to 0.51) at 52 weeks. Females (0.35, 95% C.I. = 0.18 to 0.52) had similar weight gain to males (0.37, 95% C.I. = 0.24 to 0.50) taking risperidone at 52 weeks. Female and male individuals taking quetiapine had the lowest adjusted physical weight gain across the distribution of baseline weights.

VI. DISCUSSION

In this large observational study of youth across 5 sites in the Mini-Sentinel population, we found that youth taking quetiapine had less adjusted weight gain at 52 weeks compared to youth taking aripiprazole or risperidone. The magnitude of the difference was about the same comparing quetiapine to either aripiprazole or risperidone – approximately a quarter of a standard deviation less weight gain (see **Table 19**). There was not a statistically significant difference in adjusted weight gain between the three medication exposure groups at 12 weeks. Monitoring of baseline and follow-up weights was generally suboptimal (<60%) despite clinical recommendations for routine weight monitoring in youth.

Although the baseline-to-52-week difference in adjusted weight gain for the current study was less for quetiapine relative to the other medications, all youth taking these medications gained more weight than expected due to normal growth (i.e., adjusted for age and sex using the Center for Disease Control and Prevention growth curves). At 12 weeks, youth taking aripiprazole and risperidone gained about 1/3 of a standard deviation more weight than expected and youth taking quetiapine gained about 1/5 of a standard deviation more than expected. By 52 weeks, physical weight gain was still about 1/3 of a standard deviation greater than expected among youth taking aripiprazole and risperidone but no higher for those taking quetiapine. Note that intention-to-treat estimates of standardized physical weight gain (**Table 11**) were similar for aripiprazole and risperidone, but significantly higher for quetiapine. This difference implies that the IPW adjusted the exposure to quetiapine more than the other medications.

A. COMPARISON TO PREVIOUS RESEARCH

The physical weight gain observed in the current observational study is well-aligned with the evidence from previous studies. Below, we review some of these previously reported results for aripiprazole, quetiapine and risperidone.

1. Aripiprazole

Findling and colleagues (23) conducted a 30-week, randomized, placebo-controlled study of aripiprazole for the treatment of bipolar 1 disorder in 210 youth aged 10-17 years. The authors reported change in weight z-score of 0.32 for youth taking 10 mg/day and 0.44 for youth taking 30 mg/day compared to youth randomized to placebo gaining 0.04 standard deviations in weight. In a 6-week, randomized, double-blind, placebo controlled trial of aripiprazole for treatment of schizophrenia in 302 youth, Findling and colleagues (24) reported that youth aged 13-17 years taking 10 mg/day of aripiprazole (n=100) had a mean change in weight z-score of 0.0 (zero; s.d. = 0.28). Youth taking 30 mg/day (n=102) also had a mean change in weight z-score of 0.0 (s.d. = 0.20).

Youth taking aripiprazole in our study gained comparatively similar weight to the 30-week study, but more weight than in the 6-week study. At 12 weeks, youth taking aripiprazole had a mean change in weight z-score of 0.33 (95% CI = 0.18 – 0.48) and at 52 weeks a mean change of 0.37 (95% CI = 0.11 – 0.63).) but youth in our study were also antipsychotic-free, whereas most youth in the placebo-controlled trials were taking antipsychotics at baseline that could have already resulted in relevant pre-baseline weight reducing the observable weight gain.

2. Quetiapine

Our review of the literature did not identify any randomized trials of quetiapine that reported change in weight z-scores. One double-blind, placebo controlled study (70) of quetiapine extended release reported weight gain in youth taking quetiapine of 1.3 kg in 8 weeks (s.d. = 2.14) compared to 0.6kg (s.d. = 2.39) in youth randomized to placebo. In a double-blind, placebo-controlled study of 32 youth taking quetiapine for bipolar depression, DelBello and colleagues (21) reported change in weight at 8 weeks was 2.3 kg (s.d. = 0.6) in youth taking quetiapine (n=17) and 0.9 kg (s.d. = 0.6) in the placebo group (n=15), a difference that was not significant in the small sample.

3. Risperidone

Mayaan and colleagues (71) conducted a pilot observational study of 8 youth initiating treatment with risperidone. Mean baseline weight z-score was 0.57 (s.d. = 1.35) and the mean weight z-score at 8 weeks was 0.82. Thus, the mean change in weight z-score over 8 weeks was 0.25 (s.d. = 0.30). In a randomized, double blind, 6-month, placebo-controlled trial of risperidone for the treatment of disruptive behavior in 335 youth, Reyes and colleagues (19) reported a mean change in weight z-score of 0.30 (s.d. = 0.30) at 12 weeks. By comparison, the mean change in weight z-score at 12 weeks for youth initiating risperidone in the current study was 0.32 (95% CI = 0.21, 0.44) using the treatment as delivered approach and 0.28 (95% C.I. = 0.19 to 0.38) using the intent-to-treat approach.

4. Overall

Overall, weight gain in the MSDD population of youth was somewhat lower than previously reported in a study of youth initiating SGAs conducted by Correll and colleagues.(10) That study had a final sample size of 205 patients recruited from tertiary care inpatient and outpatient settings in Queens, New York, with less than one week of antipsychotic exposure at baseline and at least one post-baseline assessment. The final analysis included 41 youth initiating aripiprazole, 45 olanzapine, 36 quetiapine, and 135 risperidone. Weight gain at a median of 10.8 weeks follow-up was 4.4 kg (95% CI, 3.7 to 5.2) in the aripiprazole group, 8.5 kg (95% CI, 7.4 to 9.7) in the olanzapine group, 6.1kg (95% CI, 4.9 to 7.2) with quetiapine, and 5.3kg (95% CI, 4.8 to 5.9) in the risperidone group. Like the present study, all youth initiating SGA medications gained significant weight at 12 weeks. In the Correll (2009) analysis, the 95% confidence interval for the weight gain observed for aripiprazole, quetiapine and risperidone overlapped - indicating that there was not a statistically significant difference in weight gain between those medications at 12 weeks.

B. STRATIFIED ANALYSES (TABLE 19) FOR BASELINE WEIGHT CATEGORY

Analyses stratified by age, sex, and baseline physical weight category largely replicated those of the main analyses. Note that the difference in change in weight z-score comparing quetiapine and aripiprazole and quetiapine to risperidone was statistically significant for males but not for females.

One potentially relevant result is the difference in mean change in weight z-score by 52 weeks stratified by baseline physical weight. Youth who were overweight at baseline and took quetiapine had less change in weight than youths who took either aripiprazole or risperidone. Among overweight youth, the difference between quetiapine and aripiprazole was -0.35 (95% C.I. = -0.58 to -0.12) and -0.37 (95% C.I. = -0.54 to -0.19) for quetiapine compared to risperidone. Thus, compared to aripiprazole and risperidone, quetiapine appears to be associated with less weight gain in youth who were overweight at baseline.

C. MISSING PHYSICAL WEIGHT MEASUREMENT

We have previously reported that baseline assessment of glucose is often missing in the MSDD population of youth initiating antipsychotic medications.(72) In that study, only 11% of youth had baseline glucose measurement. Assessment of baseline weight was better; still, only 58.5% of youth had physical weights measured at treatment initiation. Because it is recommended by clinical guidelines (73), it is somewhat heartening to note that youth with metabolic disorders were more likely to have physical weight assessed at the time that a SGA was prescribed (OR = 1.53, 95%CI = 1.32 to 1.78); however, other factors predicting physical weight assessment at baseline appear to be related to the likelihood of making any visit rather than concerted efforts by clinicians to measure weight in the population of youth initiating a SGA. Presence of a physical weight measurement was significantly higher among youth with other chronic conditions or among youth currently taking antibiotics, and these youth are more likely to make visits (and therefore have weight measured).

Monitoring of weight after initiation of antipsychotic treatment was very low. Only 25.6% of youth at 12 weeks and 54.3% at 52 weeks had physical weight recorded. Physical weight was more likely to be measured in youth taking risperidone compared to aripiprazole, but the other significant predictors were presence of chronic conditions and, again, youth with these conditions are more likely to make visits for those conditions, rather than being related to explicit monitoring of weight associated with antipsychotic use.

D. LIMITATIONS

Like any observational study, it is possible that our study results are biased due to unmeasured confounding. We used analytic techniques to attenuate potential biases in comparing physical weight change across the 3 medication groups using inverse probability weighting. However, even after controlling for treatment selection, missing physical weight measurement and censoring, important residual confounding due to patient characteristics not included in the analytic weight models could remain.

Important potential sources of this confounding may be lack of information on medication dose and knowing the particular clinical indications for which the medications were prescribed. Antipsychotic medications are used differently for treating psychoses compared to sleep disorders both in terms of dose and frequency. Correct dose information is difficult to obtain or estimate from pharmacy records. It is possible that more youth taking quetiapine were taking lower doses and only “as needed” compared to youth taking aripiprazole or risperidone. For example, low dose use of quetiapine for sleep disorders may be contributing to the lower weight gain observed at 52 weeks. Increased weight gain has been related to higher antipsychotic doses.(74)

Unfortunately, we did not have enough youth in our sample taking olanzapine to estimate inverse probability weights. This made it impossible to balance the treatment groups with respect to known confounders in comparing standardized physical weight gain estimates for olanzapine. This is somewhat reassuring as, apart from clozapine, olanzapine is known to have the highest potential for weight

gain(4), which could be why clinicians are not commonly prescribing olanzapine to youth in the MSDD population.

Furthermore, while weight measurements were conducted in relatively few youth initiating an SGA, height measurements were even fewer, precluding our reporting of BMI-z-scores. Finally, this study did not include measurements of fasting glucose and lipid metabolism, which would be ideal to assess cardiovascular morbidity and mortality risk.

VII. CONCLUSION

To our knowledge, this is the largest study of weight change in youth initiating treatment with antipsychotic medications. We applied rigorous analytic methods for estimation in observational studies to balance the medication exposure groups with respect to potentially confounding factors. Similar to previous evidence from randomized trials, we found that youth initiating treatment with antipsychotics gained statistically and clinically significantly more weight than expected due to normal growth. We also found that youth initiating treatment with quetiapine had less increase in standardized weight at 52 weeks than aripiprazole and risperidone. However, there was no difference in adjusted weight change among the 3 medications at 12 weeks. Our results argue for prioritization of weight and metabolic monitoring over antipsychotic selection.

Perhaps the strongest message from this study is that baseline and follow-up monitoring of weight in clinical care urgently needs to improve. Only a quarter of youth at 12 weeks and slightly more than half at 52 weeks had a weight measurement recorded in their clinical record. While the weight gain reported here was less than 0.5 standard deviations above that expected by normal growth (a cutoff used by obesity researchers to indicate increase in health impacts), routine monitoring of physical weight and fasting blood lipids and glucose is strongly recommended by professional guidelines (73) and necessary to ensure an acceptable risk-benefit ratio when using SGAs in youth.

VIII. APPENDICES

A. APPENDIX 1. APPROVAL DATES FOR PEDIATRIC INDICATIONS

Drug Name	Approval Date for Pediatric Indications	
Olanzapine	12/4/2009	http://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/020592Orig1s040s041Approv.pdf
Risperidone	8/22/2007	http://www.accessdata.fda.gov/drugsatfda_docs/nda/2007/020272_s046_risperdal_toc.cfm
Aripiprizole	10/29/2007 (schizophrenia)	http://www.accessdata.fda.gov/drugsatfda_docs/nda/2007/021436Orig1s017.pdf
Aripiprizole	2/27/2008 (bipolar I)	http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2008/021436s021,%20021713s016,%20021729s008,%20021866s008ltr.pdf
Quetiapine	2/2/2009	http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2009/020639s045s046ltr.pdf

B. APPENDIX 2. INTERIM MODEL RESULTS

Table 12. Treatment Selection Model Results

Covariate	Aripiprazole N=397	Quetiapine N=360
Age	**1.16 (1.11, 1.22)**	**1.19 (1.13, 1.25)**
<13 years (ref)	1	
≥ 13 years	**2.12 (1.55, 2.91)**	**2.73 (1.93, 3.87)**
Sex		
Female (ref)	1	1
Male	**0.55 (0.41, 0.74)**	**0.59 (0.43, 0.80)**
Race		
White (ref)	1	1
American Indian/Alaska native	1.57 (0.53, 4.63)	1.24 (0.40, 3.87)
Asian	0.76 (0.4, 1.44)	0.73 (0.37, 1.42)
Black/African American	**0.59 (0.36, 0.97)**	**0.44 (0.25, 0.78)**
Hawaiian/Pacific Islander	0.65 (0.23, 1.84)	1.59 (0.67, 3.78)
Unknown	1.25 (0.91, 1.72)	1.31 (0.94, 1.82)
Site		
1 (ref)	1	1
4	**1.85 (1.15, 3.00)**	0.82 (0.53, 1.27)
5	**2.39 (1.21, 4.71)**	0.96 (0.50, 1.87)
6	**3.19 (1.97, 5.15)**	**1.82 (1.19, 2.78)**
7	**4.11 (2.67, 6.31)**	1.10 (0.75, 1.61)
Prior antipsychotic use	1.75 (0.86, 3.54)	1.66 (0.80, 3.44)
Mental Health Group 1	1.11 (0.82, 1.51)	0.75 (0.54, 1.04)
Mental Health Group 2	1.53 (1.12, 2.09)	1.18 (0.85, 1.64)
Mental Health Group 3	1.11 (0.82, 1.52)	1.17 (0.85, 1.59)
Mental Health Group 4	0.89 (0.60, 1.32)	1.44 (0.99, 2.08)
Mental Health Group 5	0.67 (0.44, 1.03)	0.61 (0.38, 1.00)
Mental Health Group 6	0.67 (0.51, 0.89)	1.00 (0.74, 1.35)
Women's Health Group 2	1.15 (0.72, 1.86)	1.04 (0.64, 1.70)
Women's Health Group 3	0.78 (0.36, 1.68)	0.91 (0.43, 1.90)
Metabolic encounters Group 1	1.00 (0.77, 1.31)	0.74 (0.56, 0.98)
GI meds Group 2	0.94 (0.51, 1.72)	1.51 (0.88, 2.59)
Respiratory encounter Group 1	1.25 (0.90, 1.73)	1.31 (0.94, 1.83)
Respiratory meds Group 1	1.06 (0.77, 1.47)	0.93 (0.67, 1.31)
Neurological encounters Group 1	0.79 (0.46, 1.38)	1.03 (0.63, 1.69)
Neurological encounters Group 2	1.02 (0.78, 1.33)	1.24 (0.94, 1.63)
Neurological meds Group 1	0.81 (0.55, 1.18)	1.15 (0.81, 1.64)
Other Somatic encounters Group 1	0.86 (0.65, 1.15)	0.87 (0.65, 1.17)
Other meds assoc w/ weight gain	**1.40 (1.06, 1.86)**	**2.08 (1.54, 2.82)**
Other meds assoc w/ weight loss	**0.55 (0.40, 0.76)**	0.87 (0.62, 1.23)
Antibiotics	1.04 (0.79, 1.37)	0.81 (0.60, 1.07)
Baseline weight z-score, spline* 1	1.06 (0.77, 1.45)	0.93 (0.68, 1.27)
Baseline weight z-score, spline* 2	1.39 (0.96, 2.01)	**1.47 (1.01, 2.14)**
constant	0.10 (0.05, 0.19)	0.13 (0.07, 0.24)

*baseline weight z-score entered as a cubic spline with knots at -1, 0, and 1.

Table 13. Balance in Covariates Across Treatment Assignment (Medications)

	Unweighted			Weighted (unstabilized)			Weighted (stabilized)		
	A	Q	R	A	Q	R	A	Q	R
Numerator variables	N=397	N=359	N=1032	N=397	N=359	N=1032	N=397	N=359	N=1032
Baseline weight z-score, mean	0.35	0.32	0.09	0.16	0.25	0.19	n/a	n/a	n/a
Age, mean	14.3	14.7	11.8	13.2	13.2	12.8	n/a	n/a	n/a
Age ≥ 13 years	72.8	80.3	44.3	54.5	57.3	57.6	n/a	n/a	n/a
Male	48.9	47.5	70.3	62.4	63.0	61.5	n/a	n/a	n/a
Race									
White	61.0	59.7	58.7	61.0	59.1	59.6	n/a	n/a	n/a
Am. Indian/Alaska native	1.5	1.4	1.2	1.5	1.1	1.2	n/a	n/a	n/a
Asian	4.5	4.4	5.6	5.4	5.9	5.2	n/a	n/a	n/a
Black/African American	7.6	5.3	11.1	7.7	10.0	9.6	n/a	n/a	n/a
Hawaiian/PI	1.5	3.6	2.9	2.3	3.5	2.7	n/a	n/a	n/a
Unknown	23.9	25.6	20.5	22.1	20.4	21.8	n/a	n/a	n/a
Site									
1	9.6	24.4	21.5	23.4	24.9	20.8	n/a	n/a	n/a
4	16.9	15.8	21.4	20.0	18.3	19.9	n/a	n/a	n/a
5	6.3	6.9	7.8	7.5	7.7	7.5	n/a	n/a	n/a
6	22.9	23.9	20.8	20.6	19.9	21.6	n/a	n/a	n/a
7	44.3	28.9	28.5	28.6	29.3	30.2	n/a	n/a	n/a
Denominator-Only variables									
BL FGA or SGA use	3.5	3.9	2.6	3.3	5.0	3.8	3.0	3.3	3.3
Mental Health G1	57.9	50.8	71.0	64.0	65.9	64.0	58.6	55.5	69.1
Mental Health G2	77.3	76.7	58.0	64.3	66.0	66.0	74.3	72.8	61.2
Mental Health G3	25.4	29.4	20.5	24.8	26.1	24.4	24.8	29.2	21.4
Mental Health G4	15.1	23.1	9.3	12.3	13.4	12.8	16.4	17.9	10.1
Mental Health G 5	8.8	6.9	18.0	14.2	15.2	14.0	10.8	9.4	16.1
Mental Health G6	57.2	68.1	61.3	62.6	59.9	62.0	63.0	62.8	61.1
Women's Health G2	14.1	13.9	5.2	8.1	8.3	8.7	13.6	13.6	5.7
Women's Health G3	3.8	5.0	1.9	3.1	2.9	3.0	4.3	4.9	1.8
Metabolic encounters G1	54.7	50.8	46.7	50.8	46.7	49.2	53.5	52.5	46.6
GI meds G2	4.8	8.6	4.4	5.6	5.9	5.3	6.1	7.2	4.9
Respiratory encounter G1	24.4	27.2	20.0	20.1	20.5	22.2	23.1	23.8	22.0
Respiratory meds G1	23.2	23.9	22.3	26.7	25.3	23.2	23.5	23.9	23.1

	Unweighted			Weighted (unstabilized)			Weighted (stabilized)		
	A	Q	R	A	Q	R	A	Q	R
Neuro/Musc encounters G1	6.1	10.3	5.5	6.5	7.6	6.8	7.5	8.4	5.6
Neuro/Musc encounters G2	43.1	51.4	37.7	37.9	41.9	41.2	43.6	46.0	39.1
Neuro/Musc meds G 1	15.4	25.0	14.6	16.1	17.7	16.6	18.0	21.6	15.0
Other Somatic encounters G1	32.2	34.2	32.1	34.9	32.1	32.6	33.6	36.0	31.4
Other meds, weight gain	58.4	70.6	44.1	55.1	53.2	52.8	58.4	59.2	48.2
Other meds, weight loss	24.9	28.1	44.8	38.3	39.4	37.6	31.1	30.6	41.9
Antibiotics	46.6	45.6	43.8	45.9	43.8	45.2	46.9	47.9	43.3

Shaded cells highlight that the model achieves good balance across the medication exposure groups with respect to the known confound

Table 14. Model Predicting Measurement of Weight at 12 weeks, +/- 2 weeks

Variable	O.R.	Std. Err.	z	P>|z|	95% Conf. Int.	
Medication						
Aripiprazole (ref)	1					
Quetiapine	1.32	0.27	1.38	0.169	0.89	1.97
Risperidone	**1.50**	0.26	2.30	0.021	**1.06**	**2.12**
Age						
<13 years (ref)						
≥13 years	0.81	0.13	-1.27	0.203	0.59	1.12
Sex						
Female (ref)	1					
Male	1.05	0.16	0.31	0.758	0.77	1.42
Race						
White (ref)						
Am. Indian/Alaska Nat.	1.88	0.90	1.32	0.186	0.74	4.82
Asian	1.68	0.49	1.75	0.080	0.94	2.98
Black/African American	0.83	0.20	-0.77	0.441	0.52	1.33
Hawaiian/PI	1.23	0.52	0.48	0.629	0.53	2.82
Unknown	0.73	0.13	-1.79	0.074	0.52	1.03
Site						
1 (ref)						
4	0.89	0.20	-0.53	0.593	0.58	1.37
5	0.82	0.27	-0.61	0.540	0.43	1.55
6	1.07	0.23	0.33	0.744	0.71	1.63
7	1.25	0.24	1.16	0.247	0.86	1.82
Weight measures						
Baseline weight z-score, spline[a] 1	**0.72**	0.10	-2.26	0.024	**0.55**	**0.96**
Baseline weight z-score, spline[a] 2	**1.47**	0.26	2.18	0.029	**1.04**	**2.08**
Change in weight z-score, spline[b] 1	1.22	0.72	0.34	0.732	0.39	3.88

Variable	O.R.	Std. Err.	z	P>|z|	95% Conf. Int.	
Change in weight z-score, spline[b] 2	3.33	2.70	1.49	0.138	0.68	16.33
Interactions [c]						
change spline 1*(1-2 months)	0.65	0.64	-0.43	0.665	0.09	4.53
change spline 1*(2-3 months)	1.22	1.77	0.14	0.892	0.07	20.88
GI encounter	1.15	1.21	0.13	0.898	0.14	9.14
endpoint illness	1.64	0.57	1.40	0.160	0.82	3.26
somatic illness incident exclusion	1.17	0.88	0.21	0.832	0.27	5.09
SGA prior use	0.69	0.28	-0.91	0.365	0.31	1.54
MH Group 1	1.00	0.16	-0.02	0.986	0.72	1.37
MH Group 2	1.32	0.21	1.76	0.078	0.97	1.80
MH Group 3	1.00	0.16	-0.02	0.983	0.73	1.36
MH Group 4	0.81	0.16	-1.05	0.292	0.54	1.20
MH Group 5	1.13	0.21	0.64	0.523	0.78	1.62
MH Group 6	1.03	0.15	0.24	0.813	0.78	1.37
Contraceptives Use	1.44	0.35	1.48	0.138	0.89	2.33
Menstruation	0.73	0.31	-0.76	0.445	0.32	1.65
Metabolic Enc.	1.06	0.14	0.44	0.663	0.81	1.38
GI medication use	0.90	0.25	-0.38	0.703	0.53	1.54
Respiratory enc.	1.19	0.19	1.09	0.274	0.87	1.62
Respiratory meds.	**1.41**	0.21	2.24	0.025	**1.04**	**1.89**
Neuroological enc. 1	1.12	0.28	0.44	0.659	0.69	1.81
Neurological enc. 2	1.20	0.16	1.37	0.171	0.92	1.55
Neurologic meds. Use	1.10	0.19	0.53	0.599	0.78	1.55
Baseline somatic illness	0.87	0.12	-0.97	0.331	0.66	1.15
Weight gain meds. Use	1.19	0.17	1.17	0.241	0.89	1.58
Weight loss meds. Use	0.93	0.14	-0.49	0.628	0.69	1.25
Antibiotics Use	1.14	0.16	0.98	0.328	0.87	1.49
Constant	0.11	0.04	-6.28	0.000	0.06	0.22

[a] Baseline weight z-score entered as a cubic spline with knots at -1, 0, and 1

[b] Change in weight z-score entered as a cubic spline with knots at 0, 0.25, and 0.50.

[c] Interactions between change in weight z-score (spline), and indicators for time since weight score was measured (<1 month, ≥1 month).

Table 15. Balance Between the Overall Cohort and Cohort with Week 12 Outcome

Variable	Individuals with week 12 weight measure			
	Overall*	Unweighted	Weighted (unstabilized)	Weighted (stabilized)
Numerator variables	N=1446	N=370	N=370	N=370
Study drug				
Aripiprazole	21.4	17.6	22	n/a
Quetiapine	20.6	20.5	19.4	n/a
Risperidone	58	61.9	58.6	n/a
Age, mean	12.8	12.8	12.8	n/a
Age ≥13 years	55.4	54.1	55.4	n/a
Male	61.8	61.6	62.6	n/a
Race				

Variable	Individuals with week 12 weight measure			
	Overall*	Unweighted	Weighted (unstabilized)	Weighted (stabilized)
White	58.5	62.2	57.1	n/a
American Indian/Alaska native	1.4	2.2	1.3	n/a
Asian	5.4	7.6	5.3	n/a
Black/African American	9.9	8.7	10.2	n/a
Hawaiian/Pacific Islander	2.9	3.0	2.8	n/a
Unknown	21.9	16.5	23.3	n/a
Site				
1	18.7	18.9	18.2	n/a
4	18.5	17	19.3	n/a
5	7.2	7.0	7.5	n/a
6	23.4	21.6	23.7	n/a
7	32.2	35.4	31.3	n/a
Denominator-Only variables				
Change in z-score, mean	0.052	0.083	0.054	0.057
Baseline Antipsychotic Use	3.1	2.2	3.0	3.3
Mental Health Group 1	68.8	68.1	68.8	68.5
Mental Health Group 2	66.7	71.4	66.7	66.4
Mental Health Group 3	24.8	23.5	24.9	24.1
Mental Health Group 4	140	13.0	13.1	13.3
Mental Health Group 5	15.4	17.3	14.4	15.7
Mental Health Group 6	63.6	68.4	61.9	63.9
Women's Health Group 2	9.1	10.8	8.6	8.8
Women's Health Group 3	2.7	2.4	2.2	2.4
Metabolic encounters Group 1	57.1	58.9	55.7	56.2
GI meds Group 2	5.8	6.2	5.5	5.5
Respiratory encounter Group 1	24.5	30.3	24.3	24.8
Respiratory meds Group 1	24.2	31.4	23.9	25.6
Neuro/Musc encounters Group 1	7.1	8.7	6.8	7.2
Neuro/Musc encounters Group 2	44.1	48.9	42.3	42.9
Neuro/Musc meds Group 1	18.2	21.1	18.4	18.8
Other Somatic encounters Group 1	35.3	36.0	35.8	36.1
Other meds assoc w/ weight gain	53.9	59.2	52.7	53.5
Other meds assoc w/ weight loss	40.7	40.0	41.3	41.4
Antibiotics Use	48.2	52.7	46.6	48.0
Incident events for BL exclusions				
GI encounter	0.4	0.5	0.3	0.3
Endpoint-related illness	2.8	4.6	2.5	2.7
Somatic illness	0.6	1.1	0.6	0.8

***** Individuals not censored by the end of follow-up at 12 weeks (+/- 2 weeks)

Table 16. Balance in Covariates Between Overall Cohort and 52 Week Cohort

Variable	Individuals with Week 52 weight measure			
	Overall*	Unweighted	Weighted (unstabilized)	Weighted (stabilized)
	N=1010	N=548	N=548	N=548
Numerator variables				
Study drug				
Aripiprazole	20.1	19.3	19.5	
Quetiapine	21.3	21.4	21.3	
Risperidone	58.6	59.3	59.2	
Age, mean	12.9	12.6	12.7	
Age ≥13 years	55.6	51.8	53.7	
Male	63.0	57.7	63.0	
Race				
White	59.9	61.1	60.9	
American Indian/Alaska Nat.	0.7	0.4	0.6	
Asian	5.6	6.8	5.4	
Black/African American	10.6	11.9	10.4	
Hawaiian/Pacific Islander	2.9	2.7	2.7	
Unknown	20.3	17.2	20.0	
Site				
1	17.1	17.2	16.8	
4	18.5	16.8	18.0	
5	7.7	9.1	7.7	
6	24.4	26.5	24.3	
7	32.3	30.5	33.2	
Denominator-Only variables				
Change in z-score, mean	0.179	0.196	0.158	0.156
Baseline Prior Antipsychotic use	3.6	2.9	3.7	3.6
Mental Health Group 1	71.5	71.5	71.0	70.2
Mental Health Group 2	69.9	69.2	68.8	68.2
Mental Health Group 3	25.5	23.5	24.2	23.8
Mental Health Group 4	15.2	12.6	14.3	13.0
Mental Health Group 5	17.4	15.2	18.0	18.0
Mental Health Group 6	69.2	70.4	68.4	68.9
Women's Health Group 2	10.7	13.3	10.8	11.3
Women's Health Group 3	4.3	5.5	4.5	4.7
Metabolic encounters Group 1	67.5	69.2	66.7	66.8
GI meds Group 2	7.6	8.6	7.8	7.5
Respiratory encounter Group 1	30.7	31.8	30.0	29.7
Respiratory meds Group 1	29.3	34.3	29.4	30.0
Neuro/Musc encounters Group 1	9.7	12.8	9.7	10.1
Neuro/Musc encounters Group 2	52.7	53.1	51.9	51.0
Neuro/Musc meds Group 1	24.2	27.2	24.3	23.6
Other Somatic encounters Group 1	44.3	49.3	44.6	44.7
Other meds assoc w/ weight gain	57.1	58.6	56.5	56.0

Variable	Individuals with Week 52 weight measure			
	Overall*	Unweighted	Weighted (unstabilized)	Weighted (stabilized)
Other meds assoc w/ weight loss	45.5	48.2	45.3	45.8
Antibiotics	57.1	63.0	56.5	56.7
Incident events for BL exclusions				
GI encounter	1.9	1.6	2.1	1.9
Endpoint-related illness	6.4	6.2	6.6	6.5
Somatic illness	2.1	2.0	2.2	2.1
Eating disorder	0.5	0.6	0.4	0.4

Table 17. Results of the 12 Week Weight Gain Model (n = 369)

Variable	Coeff.	Std. Err.	z	P>|z|	95% Conf. Int.	
Study drug						
Aripiprazole	1					
Quetiapine	-0.10	0.07	-1.52	0.130	-0.24	0.03
Risperidone	0.00	0.05	-0.09	0.928	-0.11	0.10
Age (years)						
Age <13 years	1					
Age ≥13 years	-0.03	0.04	-0.79	0.432	-0.11	0.05
Sex						
Female	1					
Male	**0.14**	0.04	3.16	0.002	**0.05**	**0.22**
Race						
White (ref)	1					
American Indian/Alaska Nat.	0.10	0.08	1.26	0.210	-0.06	0.26
Asian	**-0.15**	0.07	-2.03	0.043	**-0.29**	**0.00**
Black/African American	0.03	0.07	0.43	0.670	-0.10	0.16
Hawaiian/Pacific Islander	-0.01	0.08	-0.07	0.947	-0.17	0.16
Unknown	-0.02	0.06	-0.26	0.798	-0.14	0.11
Site						
1 (ref)	1					
4	-0.08	0.06	-1.37	0.171	-0.20	0.04
5	-0.03	0.07	-0.44	0.660	-0.17	0.11
6	0.00	0.00	0.23	0.814	0.00	0.00
7	0.00	0.00	-0.09	0.932	0.00	0.00
Weight Measures						
Baseline weight z-score, spline[a] 1	-0.08	0.06	-1.37	0.171	-0.20	0.04
Baseline weight z-score, spline[a] 2	-0.03	0.07	-0.44	0.660	-0.17	0.11
Time Measures						
Time between index and BL weight measure	0.00	0.00	0.23	0.814	0.00	0.00
Time between index and 12 week weight measure	0.00	0.00	-0.09	0.932	0.00	0.00
Constant	0.24	0.22	1.06	0.289	-0.20	0.68

[a] Baseline weight z-score entered as a cubic spline with knots at -1, 0, and 1

Table 18. Results of the 52 Week Weight Gain Model (n = 548)

Variable	Coeff.	Std. Err.	z	P>|z|	95% Conf. Int.	
Study drug						
Aripiprazole (ref)	1					
Quetiapine	**-0.24**	0.10	-2.30	0.022	**-0.44**	**-0.03**
Risperidone	-0.01	0.09	-0.14	0.885	-0.20	0.17
Age						
< 13	1					
≥ 13	-0.03	0.05	-0.56	0.579	-0.13	0.07
Sex						
Female (ref)	1					
Male	-0.05	0.06	-0.85	0.396	-0.16	0.06
Race						
White (ref)	1					
American Indian/Alaska Nat.	-0.23	0.34	-0.69	0.493	-0.91	0.44
Asian	**-0.22**	0.08	-2.61	0.009	**-0.39**	**-0.05**
Black/African American	**-0.27**	0.09	-3.10	0.002	**-0.44**	**-0.10**
Hawaiian/Pacific Islander	0.16	0.13	1.24	0.216	-0.09	0.40
Unknown	0.00	0.07	-0.07	0.948	-0.14	0.13
Site						
1 (ref)	1					
4	-0.03	0.07	-0.43	0.665	-0.17	0.11
5	**-0.21**	0.09	-2.23	0.026	**-0.39**	**-0.03**
6	-0.03	0.07	-0.45	0.654	-0.18	0.11
7	-0.02	0.07	-0.28	0.779	-0.15	0.12
Weight Measures						
Baseline weight z-score, spline[a] 1	**-0.20**	0.05	-4.34	0.000	**-0.29**	**-0.11**
Baseline weight z-score, spline[a] 2	0.09	0.06	1.54	0.123	-0.02	0.20
Time Measures						
Time between index and BL weight measure	0.00	0.00	0.37	0.713	0.00	0.00
Time between index and 12 week weight measure	0.00	0.00	0.73	0.465	0.00	0.00
Constant	0.14	0.45	0.30	0.765	-0.75	1.02

[a] Baseline weight z-score entered as a cubic spline with knots at -1, 0, and 1

Table 19. Comparison of Estimated Change in Weight z-score Between Baseline and Endpoints Overall and Stratified by Age, Sex, and Weight Subgroups

	Change from Baseline, weight z-score Difference in group means		
	Quetiapine vs. Aripiprazole	Risperidone vs. Aripiprazole	Quetiapine vs. Risperidone
	mean (95% CI)	mean (95% CI)	mean (95% CI)
Outcome: 12-weeks			
OVERALL	-0.10 (-0.24, 0.03)	-0.00 (-0.11, 0.10)	-0.10 (-0.21, 0.01)
Age Subgroups			
< 13	-0.15 (-0.35, 0.04)	-0.04 (-0.21, 0.14)	-0.12 (-0.25, 0.02)
≥ 13	-0.08 (-0.25, 0.08)	0.01 (-0.11, 0.13)	-0.09 (-0.24, 0.05)
Sex Subgroups			
Female	-0.00 (-0.21, 0.20)	0.04 (-0.13, 0.21)	-0.04 (-0.21, 0.13)
Male	**-0.21 (-0.38, -0.03)**	-0.04 (-0.16, 0.09)	**-0.17 (-0.32, -0.02)**
Baseline Weight Category			
Underweight/normal	-0.11 (-0.27, 0.05)	0.04 (-0.07, 0.15)	**-0.15 (-0.29, -0.02)**
Overweight	-0.10 (-0.36, 0.16)	-0.06 (-0.30, 0.18)	-0.04 (-0.23, 0.15)
Outcome: 52-weeks			
OVERALL	**-0.24 (-0.44, -0.03)**	-0.01 (-0.20, 0.17)	**-0.22 (-0.33, -0.11)**
Age subgroups			
< 13	-0.25 (-0.56, 0.06)	-0.01 (-0.27, 0.26)	**-0.24 (-0.45, -0.04)**
≥ 13	-0.23 (-0.49, 0.03)	-0.02 (-0.26, 0.22)	**-0.21 (-0.33, -0.09)**
Sex subgroups			
Female	-0.35 (-0.62, -0.08)	-0.16 (-0.42, 0.10)	-0.19 (-0.34, -0.04)
Male	-0.08 (-0.34, 0.19)	0.14 (-0.11, 0.39)	-0.22 (-0.37, -0.07)
Baseline Weight Category			
Underweight/normal	-0.21 (-0.46, 0.04)	0.03 (-0.20, 0.25)	**-0.24 (-0.36, -0.11)**
Overweight	**-0.35 (-0.58, -0.12)**	0.02 (-0.21, 0.24)	**-0.37 (-0.54, -0.19)**

Table 20. Estimated mean Change in Weight z-score for a range of baseline z-score values.

These estimates come from the sex subgroup model

	Change from baseline, weight z-score Group means*		
	Aripiprazole	Quetiapine	Risperidone
	mean (95% CI)	mean (95% CI)	mean (95% CI)
Outcome: 12-weeks			
Female: BL z-score			
-1.0	0.23 (0.05, 0.42)	0.23 (0.06, 0.41)	0.27 (0.12, 0.42)
-0.5	0.19 (0.01, 0.37)	0.19 (0.01, 0.37)	0.23 (0.09, 0.37)
0.0	0.14 (-0.04, 0.33)	0.14 (-0.04, 0.32)	0.18 (0.04, 0.32)
0.5	0.09 (-0.10, 0.27)	0.08 (-0.08, 0.25)	0.12 (-0.01, 0.26)
1.0	0.02 (-0.17, 0.21)	0.02 (-0.13, 0.17)	0.06 (-0.08, 0.20)
1.5	-0.04 (-0.25, 0.17)	-0.05 (-0.20, 0.11)	-0.01 (-0.17, 0.16)
Male: BL z-score			
-1.0	0.46 (0.29, 0.62)	0.25 (0.08, 0.43)	0.42 (0.30, 0.54)
-0.5	0.42 (0.25, 0.58)	0.21 (0.05, 0.37)	0.38 (0.27, 0.49)
0.0	0.37 (0.20, 0.54)	0.16 (-0.00, 0.32)	0.33 (0.22, 0.44)
0.5	0.31 (0.15, 0.47)	0.10 (-0.05, 0.26)	0.27 (0.17, 0.38)
1.0	0.25 (0.09, 0.40)	0.04 (-0.11, 0.19)	0.21 (0.10, 0.32)
1.5	0.18 (0.02, 0.34)	-0.03 (-0.20, 0.15)	0.14 (0.01, 0.28)
Outcome: 52-weeks			
Female: BL z-score			
-1.0	0.68 (0.34, 1.03)	0.33 (0.14, 0.53)	0.53 (0.35, 0.70)
-0.5	0.59 (0.25, 0.93)	0.24 (0.05, 0.42)	0.43 (0.26, 0.60)
0.0	0.50 (0.17, 0.84)	0.15 (-0.03, 0.33)	0.35 (0.18, 0.52)
0.5	0.45 (0.14, 0.76)	0.10 (-0.07, 0.27)	0.29 (0.13, 0.45)
1.0	0.40 (0.11, 0.69)	0.05 (-0.11, 0.22)	0.25 (0.09, 0.40)
1.5	0.36 (0.09, 0.64)	0.01 (-0.17, 0.19)	0.21 (0.04, 0.37)
Male: BL z-score			
-1.0	0.41 (0.11, 0.70)	0.33 (0.15, 0.51)	0.55 (0.41, 0.69)
-0.5	0.31 (0.02, 0.60)	0.23 (0.06, 0.41)	0.45 (0.32, 0.59)
0.0	0.23 (-0.06, 0.51)	0.15 (-0.02, 0.32)	0.37 (0.24, 0.50)
0.5	0.17 (-0.11, 0.45)	0.09 (-0.07, 0.25)	0.31 (0.19, 0.43)
1.0	0.13 (-0.15, 0.40)	0.05 (-0.11, 0.21)	0.27 (0.15, 0.38)
1.5	0.09 (-0.19, 0.36)	0.01 (-0.16, 0.18)	0.23 (0.10, 0.36)

C. APPENDIX 3. COVARIATE DEFINITIONS

Variable	Description	Cov. #	Covariates included in variable
Baseline-only measure, was not baseline exclusion, censoring event in follow-up			
BL 1st gen antipsychotic use (***COV_1stGen***)	1st generation antipsychotic use before baseline washout period	48	1st generation antipsychotic
BL 2nd gen antipsychotic use (***COV_2ndGen***)	2nd generation antipsychotic use before baseline washout period	22 95 132 135 117	Aripiprazole Olanzapine Quetiapine Risperidone Other 2nd generation antipsychotics
Other Covariates			
Mental Health Group 1 (***BL _MHg1***)	ADD and DBD	6 64 105	ADHD, hyperkinetic syndrome Impulse control disorders Other disruptive behavior disorders
Mental Health Group 2 (***BL _MHg2***)	Depression, adjustment, acute reaction	5 86 87	Acute stress, adjustment disorder Mood disorders, major depression Mood disorders, other
Mental Health Group 3 (***BL _MHg3***)	Bipolar disorder and schizophreniform	29 136	Bipolar disorder Schizophrenia, schizophreniform disorders
Mental Health Group 4 (***BL _MHg4***)	Ethanol and other substance abuse	46 119	Ethanol, diagnosed Other substance abuse, diagnosed
Mental Health Group 5 (***BL _MHg5***)	PDD	81 124	Mental retardation Pervasive developmental disorders
Mental Health Group 6 (***BL _MHg6***)	Any other mental health diagnosis	68 143 20 123 147 69 131 152 114	Learning disability, other Sleep disorder, not organic Anxiety disorder/phobia Personality disorders Somatoform spectrum disorders Learning disorder/ dev. delay Psychiatric symptoms Tourette's disorder Other psychiatric
Women's Health Group 2 (***BL _contraceptives***)	Contraceptives	96 104 75 148 36	Oral contraceptives Other contraception Medroxyprogesterone Sterilization Contraception management
Women's Health Group 3 (***BL _menstruation***)	Menstruation issues	77 79 76 78 80	Menstruation, absence Menstruation, infrequent Menstruation, irregular Menstruation, heavy/frequent Menstruation, other disorder

Variable	Description	Cov. #	Covariates included in variable
Metabolic encounters Group 1 (***BL _METABenc***)	Metabolic conditions assoc w/ weight gain	3 159 67 82 42 57 63 61 60 106	Acanthosis nigricans Weight management program Insulin resistance/metabolic syndrome Metabolic panel Diabetes screen Hyperlipidemia screen Hypothyroidism Hypothyroid screen Hyperthyroidism Other endocrine
Respiratory encounter Group 1 (***BL _RESPenc***)	Any respiratory issue diagnosis	8 7 24 160 23 142 140 146	Anaphylaxis Allergic reaction Asthma Wheezing Asphyxia Sleep apnea Shortness of breath Smoking, diagnosed
Respiratory meds Group 1 (***BL _RESPmeds***)	Any respiratory meds	15 16 25 145	Antihistamines, non-sedating Antihistamines, other Asthma medications, other Smoking cessation medications
GI meds Group 2 (***BL _GImeds2***)	Any GI meds for minor GI issues	53 130 10 11 125	Histamine 2 receptor antagonists Proton-pump inhibitors Antacids Anti *H pylori* Phenothiazine antiemetics
Neuro/Musc encounters Group 1 (***BL _NEUROenc1***)	Any neuro dx	83 90	Migraine Neuropathic pain
Neuro/Musc encounters Group 2 (***BL _NEUROenc2***)	Any neuro injury	65	Injury, other
Neuro/Musc meds Group 1 (***BL _NEUROmeds***)	Any neuro/musc meds	84 92 88 91 39 118 115	Migraine treatment/prevention NSAID, includes coxibs Narcotic analgesic Non-narcotic analgesic Cyclobenzaprine Other skeletal muscle relaxants Other rheumatologic medications
Other Somatic encounters Group 1 (***BL _somatic***)	Any other somatic condition	158 109 74 58 112 45 34 89	Urinary tract infection Other infections Malaise and Fatigue Hypersomnia Other organic sleep disorder Edema Cholecystitis, cholelithiasis Nephrotic syndrome

Variable	Description	Cov. #	Covariates included in variable
Other meds assoc w/ weight gain (***BL_GAINmeds***)*	Other meds assoc w/ weight gain	14 37 113 72	Antidepressant Corticosteroids Other prescription dyspepsia Lithium
Other meds assoc w/ weight loss (***BL_LOSSmeds***)	Other meds assoc w/ weight loss	161 149	Weight Loss Med Stimulant
Antibiotics (***BL_antibiotics***)	(single covariate, meds)	12	Antibiotics

*incident weight gain meds were censoring events in follow-up

Baseline covariate that we computed, but not included in Model

CV meds Group 1 (***BL_CVmeds***)	Any cardiovascular med	151 4 17 102	Thiazide diuretic ACE inhibitor/ARBs Anti-hypertensives, other Other cardiovascular medications

These variables were exclusions at baseline, and time-varying covariates in the models

	Description	Cov. #	Covariates included in variable
Eating disorder (***EXCL_eatingdisorder***)	(single covariate, mental health)	44	Eating disorder
GI Encounters Group 1 (***EXCL_GIenc***)	Gastrointestinal Dx or Px	38 156 120 50 49 144 85	Crohn's Disease Ulcerative Colitis Other upper GI disease Gastric Bypass Gastric Banding Sleeve Gastrectomy Misc. Gastric Procedure

	Description	Cov. #	Covariates included in variable
Somatic Illnesses (***EXCL_somatic***)	Somatic Illness exclusions	141 40 31 30 54 52 155 97 73 133 134 47 21 35 43 70 153 154 26 139 55 127	Sicle cell disease Cystic fibrosis Cerebral palsy Cancer HIV Hepatitis B,C Tuberculosis Organ transplant Liver failure Renal dialysis/ESRD Respiratory failure Fatal metabolic disease Aplastic anemia Congenital immune deficiencies Down syndrome Lethal chromosomal abnormalities Trisomy 13 Trisomy 18 Autosomal deletion syndrome serious neuromuscular Hospice Care Prader Willi Syndrome
Endpoint-related illnesses (***EXCL_endpoint***)	Endpoint-related illness exclusions	56 41 122 18 138 137 98	Hyperlipidemia Diabetes Parkinson's Disease Antipsychotic related movement D/O Serious cardiovascular disease Seizures Organic psychotic disorder

And these were exclusions at baseline, and censoring events on follow-up

	Description	Covariates included in variable	
Women's Health Group 1 (***EXCL_preg)***	Pregnancy, perinatal conditions	128 111 121 126	Pregnancy, prior Other perinatal conditions (760-779) Ovarian cysts Polycystic Ovarian Syndrome
GI Meds Group 1 (***EXCL_GImeds1***)	GI meds used for serious GI disease	157 107	Ulcerative colitis treatment Other GI meds (azathioprine, mercaptopurine, infliximab, golimumab)

D. APPENDIX 4. COVARIATES INCLUDED IN EACH MODEL

BL=Baseline	Outcome	Model 1		Model 2		Model 3		Model 4		Model 5		Model 6 & 7	
TV=Time Varying	Models	B.L. weight		Treatment		Censor:		Censor:		Censor:		F.U. weight	
MR=Most recent	12 & 52	measured				Tx change		Disenroll		Medical		measured	
	Weeks	Den	Num	Den	Num	Den	Num	Den	Num	Den	Num	Den	Num
Time (week), spline (12,24,36 weeks)						•		•		•			
Study drug (treatment)	•		X		X	•	•	•		•	•	•	•
Age	•	•	•	•	•	•	•	•		•	•	•	•
Male	•	•	•	•	•	•	•	•		•	•	•	•
Race	•	•	•	•	•	•	•	•		•	•	•	•
Site	•	•	•	•	•	•	•	•		•	•	•	•
Baseline weight, spline (-1,0,1)	•		X	•	•	•	•	•		•	•	•	•
Change from BL weight, spline (0,0.25,0.50)						TV				TV		MR	
Time since last weight measure (varies, see notes)						X				X		X	
z-score change*time since (varies, see notes)						TV				TV		MR	
BL use FGA or SGA		BL		BL		BL						MR	
Mental Health G1		BL		BL		TV						MR	
Mental Health G2		BL		BL		TV						MR	
Mental Health G3		BL		BL		TV						MR	
Mental Health G4		BL		BL		TV						MR	
Mental Health G5		BL		BL		TV						MR	
Mental Health G6		BL		BL		TV						MR	
Women's Health (pregnancy)		BL		BL		TV						MR	
Women's Health (menstruation issues)		BL		BL		TV						MR	
Metabolic encounters G1		BL		BL		TV				BL		MR	
Gastrointestinal medication use G2		BL		BL		TV						MR	
Respiratory encounter G1		BL		BL		TV						MR	
Respiratory meds G1		BL		BL		TV						MR	
Neuro encounters G1		BL		BL		TV						MR	
Neuro encounters G2		BL		BL		TV						MR	
Neuro meds G1		BL		BL		TV						MR	
Other Somatic G1		BL		BL		TV						MR	
Other medications, weight gain		BL		BL		BL						BL	

BL=Baseline	Outcome	Model 1		Model 2		Model 3		Model 4		Model 5		Model 6 & 7	
TV=Time Varying	Models	B.L. weight		Treatment		Censor:		Censor:		Censor:		F.U. weight	
MR=Most recent	12 & 52	measured				Tx change		Disenroll		Medical		measured	
	Weeks	Den	Num	Den	Num	Den	Num	Den	Num	Den	Num	Den	Num
Other medications, weight loss		BL		BL		TV		BL		BL		MR	
Antibiotics use		BL		BL		TV						MR	
Incident events for baseline exclusions													
GI encounter						TV						MR	
Eating disorder						TV						MR*	
Endpoint-related illness						TV						MR	
Somatic illness						TV						MR	

E. APPENDIX 5. DISTRIBUTION OF WEIGHTED DISTRIBUTION*

Baseline measure	Distribution* of baseline measures by group, for those included in the final outcome models					
	Included in 12-week analysis			Included in 52-weeks analysis		
	Arip.	Quet.	Risp.	Arip.	Quet.	Risp.
	N=64	N=76	N=229	N=106	N=117	N=325
Age, mean	14.0	14.3	11.8	14.1	14.4	11.3
Baseline weight z-score	0.31	0.26	0.02	0.23	0.37	-0.04
Male	.58	.43	.69	.41	.46	.70
Race						
White	.54	.63	.62	.59	.65	.58
Am. Indian/Alaska Nat.	.02	.03	.01	.01	--	.00
Asian	.08	.12	.07	.06	.05	.06
Black/African American	.14	.04	.09	.06	.05	.15
Hawaiian/PI	.01	.03	.03	.01	.06	.03
Unknown	.21	.18	.18	.27	.20	.18
Site						
1	.09	.26	.22	.14	.24	.16
4	.15	.11	.19	.12	.12	.20
5	.08	.08	.07	.07	.10	.10
6	.33	.21	.19	.22	.22	.28
7	.35	.34	.33	.45	.31	.25
Antipsychotic prior	.04	.09	.03	.03	.04	.04
Mental Health G1	.67	.46	.70	.58	.47	.71
Mental Health G2	.73	.65	.58	.72	.64	.54
Mental Health G3	.23	.26	.17	.19	.27	.17
Mental Health G4	.10	.12	.14	.13	.16	.05
Mental Health G5	.19	.12	.15	.13	.12	.22
Mental Health G6	.54	.66	.59	.60	.63	.59
Women's Health G2	.08	.13	.05	.19	.06	.04
Women's Health G3	--	.02	.01	.03	.04	.01
Metabolic encounters G1	.49	.47	.38	.53	.38	.43
GI meds G2	.04	.07	.05	.08	.06	.03
Respiratory encounter G1	.14	.19	.22	.19	.19	.21
Respiratory meds G1	.17	.29	.21	.22	.22	.19
Neuro/Musc enc. G1	.09	.08	.04	.06	.09	.05
Neuro/Musc enc. G2	.40	.43	.34	.35	.36	.35
Neuro/Musc meds G1	.11	.18	.16	.13	.19	.09
Other Somatic enc. G 1	.22	.24	.31	.35	.27	.25
Meds, weight gain	.62	.67	.49	.69	.68	.51
Meds, weight loss	.40	.25	.42	.32	.27	.43
Antibiotics Use	.34	.43	.39	.37	.39	.37

*Weighted using stabilized weights, truncated at 10 (these are the weights used in the analysis).

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