

Continuation of Atypical Antipsychotic Medication during Early Pregnancy and the Risk of Gestational Diabetes

Electronic supplement materials

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Figure S1. Study design, exposure definition, and outcome definition

Figure S2. Flow chart illustrating the cohort creation process for each antipsychotic exposure group

Table S1. All patient characteristics comparing continuers to discontinuers of each atypical antipsychotic medication, unadjusted

	Aripiprazole			Ziprasidone			Quetiapine			Risperidone			Olanzapine			
	Group N ^a	Cont. 419 %	Disc. 1505 %	SDiff	Cont. 167 %	Disc. 506 %	SDiff	Cont. 1543 %	Disc. 2990 %	SDiff	Cont. 359 %	Disc. 1465 %	SDiff	Cont. 384 %	Disc. 1041 %	SDiff
Demographics																
Age <20		30.1	36.0	0.13	16.2	25.5	0.23	15.6	26.0	0.26	29.2	32.4	0.07	10.2	18.1	0.23
Age 20 to <30		43.7	48.6	0.10	61.7	56.3	0.11	50.7	54.7	0.08	40.9	51.8	0.22	45.6	60.1	0.30
Age 30 to <40		22.7	14.4	0.22	18.6	17.2	0.04	30.9	18.0	0.31	27.6	14.8	0.32	40.1	20.0	0.45
Age > 40		3.6	1.0	0.17	3.6	1.0	0.18	2.8	1.3	0.10	2.2	1.0	0.10	4.2	1.8	0.14
White		66.3	65.4	0.02	69.5	67.8	0.04	72.5	68.3	0.09	49.0	54.5	0.11	50.8	61.2	0.21
Black		19.6	18.6	0.03	19.2	21.3	0.05	15.4	17.2	0.05	30.4	30.2	0.00	24.2	22.8	0.03
Other race		14.1	15.9	0.05	11.4	10.9	0.02	12.1	14.5	0.07	20.6	15.3	0.14	25.0	16.0	0.22
Eligibility ^b at baseline		15.3	18.2	0.08	7.2	16.2	0.28	9.6	12.0	0.08	9.2	13.4	0.13	3.6	8.9	0.22
Eligibility ^b before delivery		18.6	22.5	0.10	15.0	19.0	0.11	15.9	19.4	0.09	14.2	18.0	0.10	8.6	15.3	0.21
Mental health diagnosis																
ADHD		9.3	11.8	0.08	10.2	8.3	0.07	8.4	7.9	0.02	15.6	9.8	0.18	4.4	4.8	0.02
Bipolar disorder		44.6	38.4	0.13	45.5	37.7	0.16	36.0	27.5	0.18	25.1	23.8	0.03	32.0	28.9	0.07
Schizophrenia/Other psychoses		10.0	7.2	0.10	19.2	9.9	0.27	7.4	5.1	0.10	18.7	10.7	0.23	24.7	9.8	0.40
Other psychiatric disorders		11.5	7.9	0.12	8.4	9.3	0.03	8.7	10.2	0.05	7.5	9.4	0.07	6.8	8.5	0.07
Depression		39.1	38.2	0.02	39.5	37.7	0.04	42.9	43.2	0.01	44.8	44.5	0.01	38.0	39.7	0.03
Anxiety disorder		24.8	20.8	0.10	21.6	22.5	0.02	28.7	22.9	0.13	20.1	20.3	0.01	20.6	20.9	0.01
Comorbidity																
Prior GDM ^b		4.8	4.3	0.03	2.4	7.1	0.22	4.9	4.3	0.03	3.1	2.6	0.03	2.9	3.2	0.02
Any pain disorder		40.3	36.3	0.08	42.5	42.3	0.01	45.4	38.6	0.14	31.5	32.7	0.03	32.3	38.6	0.13
Hypertension		4.8	2.8	0.10	4.8	3.0	0.10	5.2	3.4	0.09	3.6	3.4	0.01	3.9	3.7	0.01
Obesity		5.3	3.7	0.07	4.8	3.4	0.07	2.3	2.6	0.02	2.2	2.5	0.02	2.3	1.4	0.07
Dyslipidemia		3.6	1.7	0.12	4.8	1.4	0.20	2.1	1.5	0.05	0.8	1.2	0.04	3.4	1.7	0.11
Other medication use																
Anticonvulsants		33.2	24.4	0.20	33.5	28.3	0.11	36.4	27.5	0.19	31.5	23.9	0.17	25.3	18.4	0.17
Antidepressants		71.8	63.2	0.19	73.7	65.8	0.17	75.6	68.0	0.17	71.9	68.4	0.08	70.1	65.6	0.10
Anxiolytics		3.3	3.5	0.01	3.6	4.7	0.06	5.1	3.6	0.07	2.8	2.8	0.00	2.1	3.7	0.10
Benzodiazepines		34.1	20.9	0.30	41.9	24.3	0.38	39.4	23.2	0.36	24.5	17.7	0.17	29.7	22.2	0.17
Mood stabilizers ^c		30.1	23.5	0.15	31.7	27.5	0.09	31.8	26.0	0.13	30.1	22.7	0.17	21.6	18.1	0.09
Opioids		36.0	34.3	0.04	40.1	39.1	0.02	46.7	37.9	0.18	28.4	28.9	0.01	32.6	34.4	0.04
Other hypnotics		24.1	15.3	0.22	28.1	17.4	0.26	20.6	16.3	0.11	13.6	13.9	0.01	17.7	14.5	0.09
Stimulants		15.5	12.2	0.10	15.6	7.3	0.26	11.5	8.8	0.09	18.9	9.6	0.27	4.2	3.7	0.03
Antihypertensives		10.0	6.1	0.14	10.2	3.8	0.25	10.7	6.6	0.15	8.9	7.2	0.06	5.5	6.3	0.04

Health service utilization in 90 days before LMP

Median N generic drug	8	7	0.23	9	8	0.23	9	8	0.25	7	7	0.11	7	7	0.01
Median N ED visits	1	1	0.09	1	1	0.06	1	1	0.00	0	1	0.19	0	1	0.14

Duration of antipsychotic use during 90 days before LMP

Exposed ≤30 days	20.0	52.6	0.72	15.6	56.7	0.95	19.2	50.1	0.68	26.7	57.0	0.64	20.1	59.2	0.87
Exposed >30 days, ≤60 days	30.5	29.2	0.03	21.6	26.5	0.12	20.2	29.9	0.23	27.9	29.9	0.05	25.3	27.2	0.04
Exposed >60 days	49.4	18.1	0.70	62.9	16.8	1.07	60.5	20.0	0.91	45.4	13.1	0.76	54.7	13.6	0.96

^a Number of subject in each group before trimming and stratification

^b The presence of a diagnosis of GDM in a previous pregnancy was assessed based on all available data before the start of the index pregnancy

^c Mood stabilizers: Lithium, Carbamazepine, divalproex, lamotrigine, oxcarbazepine, topiramate, valproic acid, valproate sodium

Cont: Continuers; Disc: Discontinuers; SDiff: standardized difference; ADHD: attention-deficit hyperactivity disorder; GDM: gestational diabetes; ED: emergency department; LMP: last menstrual period
Variable formats as used in the propensity score model

Table S2. All patient characteristics comparing continuers to discontinuers of each atypical antipsychotic medication, weighted by propensity score

	Aripiprazole			Ziprasidone			Quetiapine			Risperidone			Olanzapine			
	Group N ^a	Cont. 416	Disc. 1421	Cont. 140	Disc. 431	SDiff	Cont. 1542	Disc. 2951	SDiff	Cont. 343	Disc. 1449	SDiff	Cont. 375	Disc. 978	SDiff	
		%	%	%	%		%	%		%	%		%	%		
Demographics																
Age <20		30.3	31.7	0.03	18.6	18.3	0.01	15.6	15.4	0.00	29.2	27.9	0.03	10.4	11.5	0.04
Age 20 to <30		44.0	44.3	0.01	58.6	61.7	0.06	50.8	51.5	0.02	42.0	40.8	0.02	45.6	50.9	0.11
Age 30 to <40		22.4	21.0	0.03	20.7	18.8	0.05	30.9	30.7	0.00	26.8	27.8	0.02	39.7	35.2	0.10
Age > 40		3.4	2.9	0.03	2.1	1.2	0.07	2.8	2.4	0.03	2.0	3.5	0.09	4.3	2.5	0.10
White		66.6	68.6	0.04	67.9	68.2	0.01	72.4	72.5	0.00	49.3	50.3	0.02	51.2	52.6	0.03
Black		19.7	19.2	0.01	20.7	21.0	0.01	15.4	16.0	0.01	30.3	30.9	0.01	24.5	23.4	0.03
Other race		13.7	12.3	0.04	11.4	10.8	0.02	12.1	11.5	0.02	20.4	18.8	0.04	24.3	24.1	0.01
Eligibility (poverty) at baseline		15.4	16.5	0.03	8.6	7.5	0.04	9.6	10.2	0.02	9.6	10.4	0.03	3.7	4.2	0.03
Eligibility (poverty) before delivery		18.8	19.9	0.03	15.7	17.9	0.06	16.0	15.4	0.01	14.3	13.4	0.03	8.8	8.4	0.02
Mental health diagnosis																
ADHD		9.4	9.2	0.01	10.7	10.0	0.02	8.3	8.3	0.00	14.9	15.0	0.00	4.5	5.3	0.03
Bipolar disorder		44.5	45.0	0.01	44.3	45.2	0.02	35.9	35.3	0.01	25.1	25.6	0.01	31.7	41.9	0.21
Schizophrenia/Other psychoses		10.1	10.7	0.02	17.1	17.8	0.02	7.4	8.2	0.03	17.8	18.7	0.02	22.9	24.1	0.03
Other psychiatric disorders		11.3	12.7	0.05	7.9	10.9	0.11	8.7	9.6	0.03	7.3	7.3	0.00	6.9	7.0	0.00
Depression		39.2	38.0	0.02	41.4	39.8	0.03	42.9	43.7	0.02	44.3	45.6	0.03	38.7	39.3	0.01
Anxiety disorder		24.8	25.9	0.03	22.1	22.6	0.01	28.7	29.5	0.02	19.8	19.3	0.01	20.8	24.1	0.08
Comorbidity																
Prior GDM ^b		4.8	4.7	0.00	2.1	1.6	0.04	4.9	5.2	0.01	3.2	2.8	0.02	2.9	1.5	0.09
Any pain disorder		39.9	41.1	0.03	42.1	43.1	0.02	45.4	45.9	0.01	30.9	32.9	0.04	32.0	32.4	0.01
Hypertension		4.3	4.0	0.02	3.6	5.4	0.09	5.2	4.8	0.02	3.8	4.3	0.03	3.7	2.6	0.06
Obesity		5.3	4.6	0.03	3.6	4.5	0.05	2.3	2.2	0.01	2.3	1.7	0.05	2.4	0.7	0.14
Dyslipidemia		3.4	2.4	0.06	2.1	1.8	0.02	2.1	2.7	0.04	0.9	1.1	0.02	2.9	1.6	0.09
Other medication use																
Anticonvulsants		32.7	31.6	0.02	32.1	37.1	0.11	36.4	36.8	0.01	29.4	30.4	0.02	25.1	30.1	0.11
Antidepressants		71.6	71.8	0.00	73.6	72.4	0.03	75.6	75.5	0.00	72.6	72.2	0.01	70.7	71.2	0.01
Anxiolytics		3.4	3.0	0.02	4.3	8.8	0.18	5.0	5.3	0.02	2.6	2.7	0.00	2.1	2.1	0.01
Benzodiazepines		33.7	35.2	0.03	39.3	40.5	0.02	39.4	38.9	0.01	23.6	24.7	0.03	29.1	31.3	0.05
Mood stabilizers ^c		29.6	28.9	0.01	31.4	35.4	0.09	31.8	31.3	0.01	28.6	32.1	0.08	21.3	26.5	0.12
Opioids		35.8	38.1	0.05	40.7	40.3	0.01	46.7	47.1	0.01	27.4	27.7	0.01	32.8	34.1	0.03
Other hypnotics		23.8	25.2	0.03	27.9	27.3	0.01	20.6	21.0	0.01	14.0	13.7	0.01	17.6	19.7	0.06
Stimulants		15.4	14.9	0.01	14.3	13.3	0.03	11.4	11.2	0.01	17.8	17.5	0.01	4.3	3.9	0.02

Antihypertensives	9.6	12.2	0.08	7.1	11.6	0.15	10.7	11.5	0.02	9.0	11.0	0.07	5.3	5.6	0.01
Health service utilization in 90 days before LMP															
Median N generic drug	8	7	0.03	7	8	0.12	9	9	0.01	7	8	0.01	7	7	0.09
Median N ED visits	1	1	0.02	1	1	0.07	1	1	0.01	0	0	0.07	0	1	0.05
Duration of antipsychotic use during 90 days before LMP															
Exposed ≤30 days	20.2	20.0	0.01	18.6	17.3	0.03	19.3	19.3	0.00	27.7	28.0	0.01	20.5	21.0	0.01
Exposed >30 days, ≤60 days	30.8	31.2	0.01	23.6	25.8	0.05	20.2	20.4	0.01	28.9	29.9	0.02	25.9	23.6	0.05
Exposed >60 days	49.0	48.8	0.00	57.9	56.9	0.02	60.5	60.2	0.01	43.4	42.1	0.03	53.6	55.4	0.04

^a Number of subject in each group after trimming and stratification

^b The presence of a diagnosis of GDM in a previous pregnancy was assessed based on all available data before the start of the index pregnancy

Bolded cells: Absolute Standardized difference > 0.1 after propensity score weighting.

^c Mood stabilizers: Lithium, Carbamazepine, divalproex, lamotrigine, oxcarbazepine, topiramate, valproic acid, valproate sodium

Cont: Continuers; Disc: Discontinuers; SDiff: standardized difference; ADHD: attention-deficit hyperactivity disorder; GDM: gestational diabetes; ED: emergency department; LMP: last menstrual period

Table S3. Results from additional analyses based on the risk-stratified groups, comparing continuers to discontinuers with respect to the risk of gestational diabetes

Groups/ Analysis	N	Case (n)	Risk	Unadjusted		Adjusted		
				RR	95% CI	RR	95% CI	
Low risk group								
Restricted	Continuer	440	19	4.3%	0.83	(0.51, 1.37)	0.68	(0.41, 1.11)
	Discontinuer	1333	69	5.2%				
6-month baseline	Continuer	408	19	4.7%	1.03	(0.62, 1.71)	0.72	(0.44, 1.19)
	Discontinuer	1261	57	4.5%				
12-month baseline	Continuer	306	15	4.9%	1.14	(0.64, 2.02)	1.03	(0.57, 1.85)
	Discontinuer	973	42	4.3%				
hdPS adjusted ^a							0.80	(0.52, 1.24)
Medium risk group								
Restricted	Continuer	1304	91	7.0%	1.67	(1.28, 2.18)	1.25	(0.97, 1.61)
	Discontinuer	2778	116	4.2%				
6-month baseline	Continuer	1291	93	7.2%	1.76	(1.35, 2.27)	1.46	(1.14, 1.87)
	Discontinuer	3119	128	4.1%				
12-month baseline	Continuer	993	61	6.1%	1.44	(1.06, 1.96)	1.21	(0.90, 1.64)
	Discontinuer	2388	102	4.3%				
hdPS adjusted							1.27	(1.04, 1.56)
High risk group								
Restricted	Continuer	274	36	13.1%	2.84	(1.78, 4.53)	1.84	(1.14, 2.96)
	Discontinuer	626	29	4.6%				
6-month baseline	Continuer	291	34	11.7%	2.47	(1.58, 3.87)	1.72	(1.09, 2.71)
	Discontinuer	762	36	4.7%				
12-month baseline	Continuer	226	26	11.5%	2.86	(1.68, 4.88)	3.39	(1.83, 6.27)
	Discontinuer	597	24	4.0%				
hdPS adjusted							1.33	(0.93, 1.91)

^a hdPS adjusted: stratification adjustment using 50 additional confounder proxy variables in propensity score estimation

RR: relative risks; CI: confidence interval; hdPS: high-dimensional propensity score

Table S4. The difference in obesity prevalence between continuers and discontinuers of olanzapine or quetiapine used in the sensitivity analysis

Olanzapine					ALB=1.13	ARR=1.61	AUB=2.29
P_E	P_{C1}	P_{C0}	P_C	P_{diff}		RR₂	RR₃
0.27	0.45	0.68	0.62	-0.23	1.47	2.09	2.97
0.27	0.5	0.66	0.62	-0.16	1.35	1.93	2.74
0.27	0.55	0.65	0.62	-0.10	1.25	1.78	2.54
0.27	0.6	0.63	0.62	-0.03	1.16	1.66	2.36
0.27	0.65	0.61	0.62	0.04	1.08	1.54	2.19
0.27	0.7	0.59	0.62	0.11	1.01	1.44	2.05
0.27	0.75	0.57	0.62	0.18	0.94	1.35	1.91
0.27	0.8	0.55	0.62	0.25	0.88	1.26	1.79

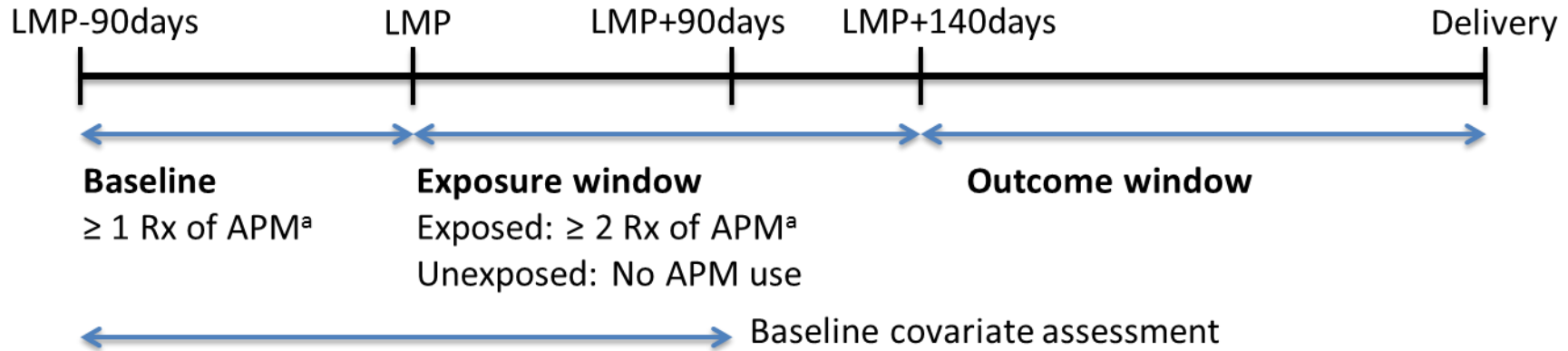
Quetiapine					ALB=1.01	ARR=1.28	AUB=1.62
P_E	P_{C1}	P_{C0}	P_C	P_{diff}	RR₁	RR₂	RR₃
0.34	0.45	0.71	0.62	-0.26	1.34	1.70	2.15
0.34	0.5	0.68	0.62	-0.18	1.23	1.56	1.97
0.34	0.55	0.66	0.62	-0.11	1.13	1.43	1.81
0.34	0.6	0.63	0.62	-0.03	1.04	1.32	1.67
0.34	0.65	0.60	0.62	0.05	0.96	1.22	1.55
0.34	0.7	0.58	0.62	0.12	0.89	1.13	1.43
0.34	0.75	0.55	0.62	0.20	0.83	1.05	1.33
0.34	0.8	0.53	0.62	0.27	0.77	0.97	1.23

RR= relative risk adjusted for obesity, ARR = apparent RR before adjusting for obesity, ALB = apparent lower bound, AUB = apparent upper bound, P_E = prevalence of continuers, P_{C1} = obesity prevalence among the exposed, P_{C0} = obesity prevalence among the unexposed, P_C = obesity prevalence in the entire population (fixed at 0.62), and P_{diff} = P_{C1} - P_{C0}.

The strength of association between obesity and the risk of gestational diabetes (RR_{CD}) is assumed to be 4.

Each boxed row represents the combination of parameters that corrects the ARR close to 1.00.

Figure S1. Study design, exposure definition, and outcome definition



	Gestational diabetes (case definition)	Pre-gestational diabetes (excluded)
Based on the algorithm^b	<p>≥ 2 diagnosis codes (250.x, 648.0x, 648.8x) on different dates from LMP+141 to delivery <i>and</i> meet the following conditions:</p> <p>No diabetes diagnosis, GTT, or treatment between LMP and LMP+140 and <i>either</i></p> <ol style="list-style-type: none"> GTT between LMP+141 and delivery <i>or</i> No GTT at any time but have at least one GDM diagnosis (648.8x) between LMP+141 and delivery 	<p>≥ 2 diagnosis codes (250.x, 648.0x, 648.8x) on different dates from LMP to delivery <i>and</i></p> <p>Those who do not meet the case definition of gestational diabetes (i.e. received diagnosis, GTT, or treatment for diabetes between LMP and LMP+140 or only have diagnoses for pre-existing diabetes without a GTT)</p>
Additional exclusion		1 diagnosis code (250.x, 648.0x, 648.8x) or diabetes treatment without a diagnosis code using the baseline covariate definitions

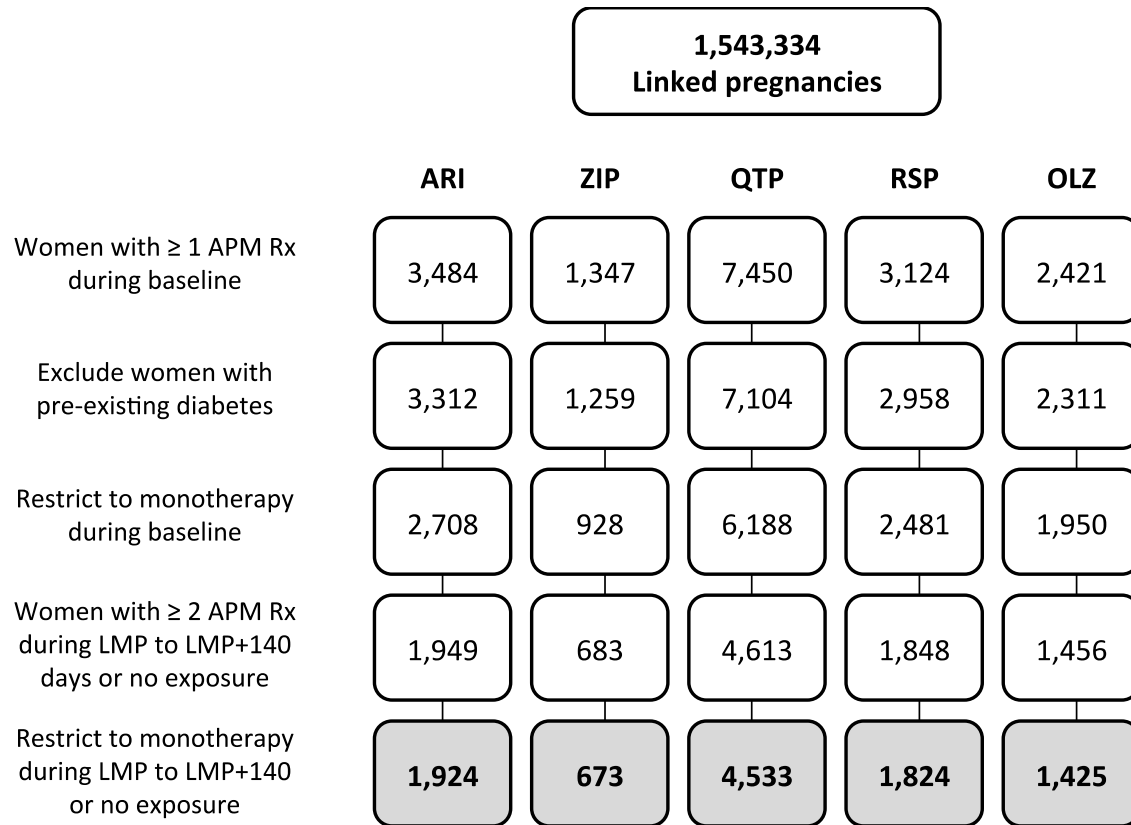
LMP: Last menstrual period; Rx: prescription; APM: Antipsychotic; GTT: glucose tolerance test

^a Restricted to use of a single antipsychotic agent during baseline and exposure window

^b In the original algorithm by Andrade et al, exclusion was based on LMP+90 days rather than LMP+140 days. It was modified to meet our exposure definition and also to make the case definition more specific

Following algorithm by Andrade et al., We excluded women with two or more diagnoses of any diabetes (gestational or pre-gestational, ICD-9 code 250.x, 648.0x, 648.8x) who received the first diagnosis, glucose tolerance test (GTT), or diabetes treatment before or on day 140 of pregnancy (i.e. the first 20 weeks). The algorithm was based on the expectation that women with known pre-existing diabetes are unlikely to receive GTT. As a modification to the algorithm, we further excluded women with only one diagnosis or who received diabetes treatment without a diabetes diagnosis.

Figure S2. Flow chart illustrating the cohort creation process for each antipsychotic exposure group



ARI: aripiprazole; QTP: quetiapine; RSP: risperidone; ZIP: ziprasidone; OLZ: olanzapine
 APM: antipsychotics; Rx: prescription; LMP: last menstrual period