

## Supplementary Online Content

Mezzacappa A, Lasica P-A, Gianfagna F, et al. Risk for autism spectrum disorders according to period of prenatal antidepressant exposure: a systematic review and meta-analysis. *JAMA Pediatr.* Published online April 17, 2017. doi:10.1001/jamapediatrics.2017.0124

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This supplementary material has been provided by the authors to give readers additional information about their work.

**eTable.** Description of the Studies on Antidepressant Exposure During Pregnancy and ASD

Study	Design	Period	Population	Sample size	Country	Inclusion criteria	Exclusion criteria	Control group	Exposure
Boukhris et al, 2015	Cohort	01/01/1998-31/12/2009	Québec Children/Pregnancy Cohort.	145,456	Canada	Singletons born between 98/01/01 and 09/12/31, ≥37weeks' gestation. Mothers covered by the RAMQ drug plan 12 months minimum before and during pregnancy.	-	Infants not exposed in utero to AD.	At least 1 prescription during pregnancy or a prescription before pregnancy overlapping with the first day of gestation.
Hviid et al, 2013	Cohort	1996-2010	Danish Medical Birth Registry; Danish National Prescription Registry; Danish Psychiatric Central Register; Danish Civil Registration System	626875	Denmark	Singletons born in Denmark between 96/01/01 and 05/12/31; with gestational age known.	Children with genetic conditions: fragile X syndrome, tuberous sclerosis, Angelman's syndrome, Down's syndrome, DiGeorge's syndrome, neurofibromatosis, Prader-Willi syndrome; Congenital rubella syndrome.	Children of mothers without SSRI prescriptions from 2 years before pregnancy through delivery	SSRI use from 4 weeks before the beginning of the pregnancy until delivery.

Study	Design	Period	Population	Sample size	Country	Inclusion criteria	Exclusion criteria	Control group	Exposure
Sorensen et al, 2013	Cohort	1995-2010	Danish Medical Birth Registry; Danish National Prescription Registry; Danish Psychiatric Central Register; Danish Civil Registration System; Danish National Hospital Register	655 615	Denmark	Children with ICD-10: F84.0, F84.1, F84.5, F84.8, F84.9. Time of conception after 96/02/01. Antidepressant drugs with ATC code N06A with exposure window from 30 days before conception to the day of birth,	Children with extreme (or missing) values for gestational age ( $\leq 23$ weeks and $\geq 45$ weeks). Missing information about mothers. Adopted children. Children who died during the first year of life. Children who emigrated.	Children of mothers without AD prescriptions from 30 days before conception to delivery	Antidepressant use from 30 days before conception to delivery
Castro et al, 2016	Case-control	1997-2010	Partners HealthCare system; the Beth Israel Deaconess Medical Center, the Boston Children's Hospital, Massachusetts Registry of Vital Records and Statistics.	1245 cases – 3405 controls	United States	Children aged of 2 – 19 years. One ICD-9 code of 299 (pervasive developmental disorder) between 1997 and 2010. Delivered at MGH, BWH, NWH or BIDMC.	Children with ASD not having a match in the control population.	Non-ASD children delivered at MGH, BWH, NWH or BIDMC with the same year of birth, birth hospital, sex, insurance type as a proxy for socioeconomic status, ethnicity and preterm versus full-term status, matched at a ratio of 3 controls per case	Exposure during pregnancy (from the 90 days before last menstrual period (LMP) through delivery) and before pregnancy (any time before LMP)

Study	Design	Period	Population	Sample size	Country	Inclusion criteria	Exclusion criteria	Control group	Exposure
Clements et al, 2015	Case-control	1997-2010	The Partners HealthCare electronic health record: Massachusetts General Hospital (MGH), Brigham and Women's Hospital (BWH), Newton-Wellesley Hospital (NWH), as well as from community and specialty hospitals which are part of the Partners HealthCare system, and affiliated outpatient clinics.	1377 cases – 4022 controls	United States	Children aged of 2 – 19 years. One ICD-9 code of 299 (pervasive developmental disorder) between 1997 and 2010. Delivered at MGH, BWH, NWH.	Unconfirmable mother-child matches.	Non-ASD control children delivered at MGH, BWH, or NWH with the same year of birth, birth hospital, sex, insurance type as a proxy for socioeconomic status, race/ethnicity, and preterm versus full-term status. No prior history of ASD, ADHD, or intellectual disability (ICD9 of 299, 314, or 317–319) Matched at a ratio of 3 controls per case.	Antidepressant use at any time during pregnancy

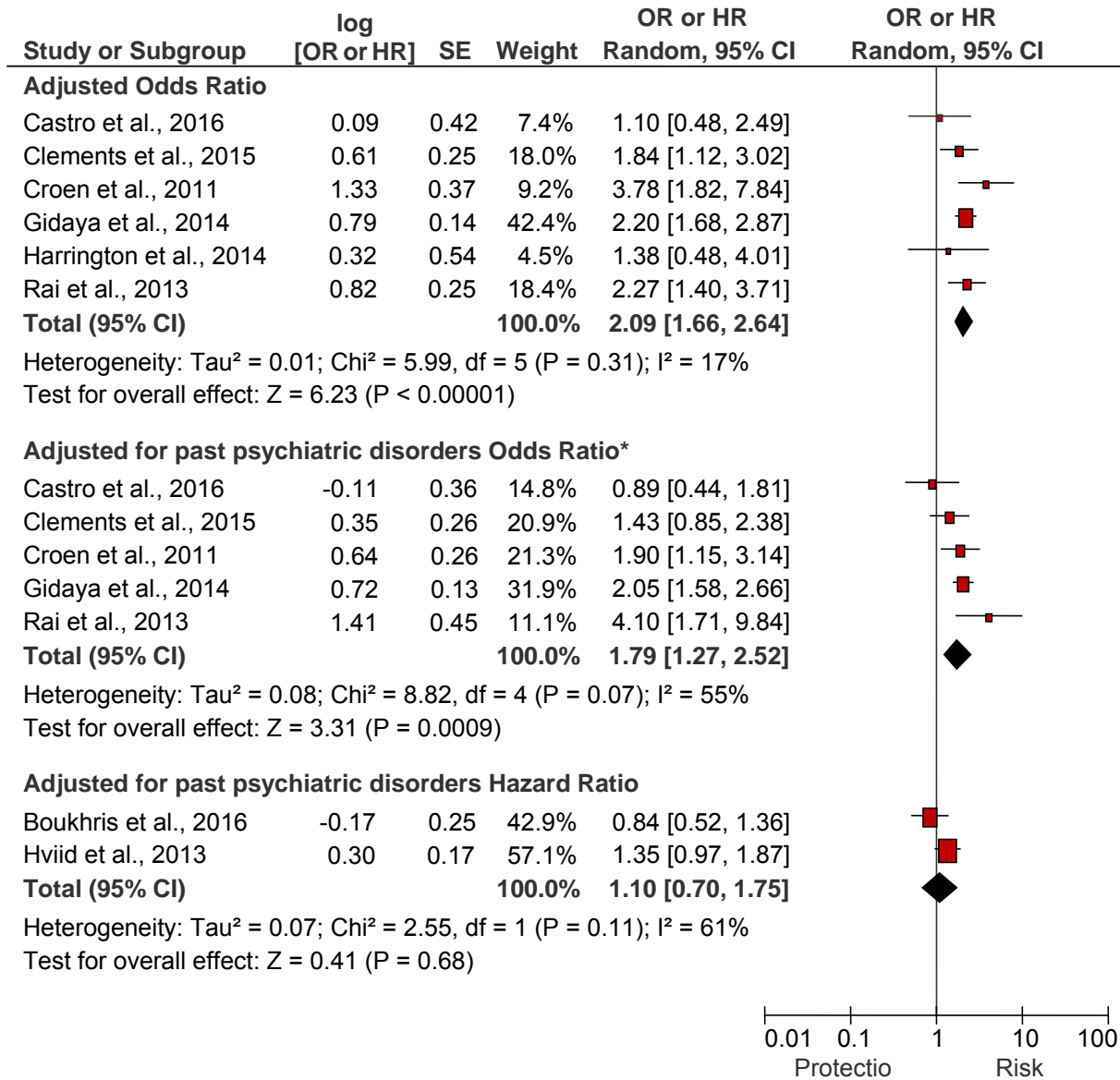
Study	Design	Period	Population	Sample size	Country	Inclusion criteria	Exclusion criteria	Control group	Exposure
Gidaya et al, 2014	Case-control	1997-2011	Danish Drug Prescription Register; Danish Psychiatric Central Register; Danish Civil Registration System; Danish National Hospital Register	57365	Denmark	Children born in Denmark between 97/01/01 and 06/12/3. Singletons or one child randomly selected from multiple births. Subjects' records from 99/01/01 to 11/03/31 were searched for ICD-10 code F840, F841, F845, F848, and F849	Children not linked to biological mother. Mother not living in Denmark one year before delivery. Child's gestational age <23 weeks or >43 weeks.	Children from the Danish Civil Registration System without ASD admission diagnoses. 10 controls per case individually matched for birth month and year	SSRI use from 3 months prior to the estimated date of conception to delivery
Harrington et al, 2014	Case-control	2003-2010	CHARGE Standardized telephone interview	812	United States	Children 2–5 years old, born in California and at least one parent who speaks English or Spanish, diagnosed with ASD or other developmental disorders. Living with at least one biological parent and in catchment area of specified California Regional Centers that coordinate services for those with developmental disabilities	Siblings of probands.	Children identified using state birth files Matched with autism cases for age, sex and regional center (targeted 4:1 male to female ratio).	SSRI use 3 months before conception to delivery.

Study	Design	Period	Population	Sample size	Country	Inclusion criteria	Exclusion criteria	Control group	Exposure
Rai et al, 2013	Case-control	2001-2007	Stockholm Youth Cohort; Swedish National and Regional Register; Stockholm County Adult Psychiatric Outpatient Register; Swedish medical birth register.	47706	Sweden	All children 0–17 years old, residing in Stockholm County between 2001 and 2007. With ASD defined by codes from the ICD-9 (299) and ICD-10 (F84), DSM-IV, (299).	Missing maternal identification numbers. Adopted children. Living in Stockholm County for less than 4 years.	Children in Stockholm Youth Cohort without ASD diagnosis. Matched for sex, birth month and birth year in a ratio of 1 case to 10 controls	SSRI use reported by mothers at their first antenatal interview.
Eriksson et al, 2012	Case-control	2002-2008	Autism Center for Young Children in Stockholm; Swedish medical birth register; Statistical Central Bureau of Sweden	173578	Sweden	Children born between 2002 and 2006. Registered with a clinical diagnosis of ASD between 2005 and 2008 in the county.	Non Swedish or English speaking families. Children who emigrated. Children referred to general rehabilitation centers due to complex needs in addition to ASD. Families who declined invitation.	Children born in Stockholm County between 2002–2006 without a clinical diagnosis of ASD.	Antidepressant use during pregnancy.

Study	Design	Period	Population	Sample size	Country	Inclusion criteria	Exclusion criteria	Control group	Exposure
Croen et al, 2011	Case-control	1995-2002	Kaiser Permanente Medical Care Program in Northern California (KPNC)	1805	United States	Children born in KPNC facility between January 1995 and June 1999. With at least 1 diagnosis of autism (ICD-9-CM code 299.0), Asperger's syndrome (ICD-9-CM code 299.8), pervasive developmental disorder not otherwise specified (ICD-9-CM code 299.8). One child per mother. Mothers were KPNC members with full pharmacy benefits in the year before delivery. Remained in health plan for at least 2 years following birth.	Medical records contained an ASD diagnosis recorded after initial control selection	Children without an ASD diagnosis from the cohort randomly sampled. Matched at a ratio of 5 controls per case, for sex, birth year and hospital of birth.	SSRI prescription for mothers in the year prior to delivery.

Legend: AD=Antidepressants ; ASD=Autism Spectrum Disorder ; SSRI=Selective Serotonin Reuptake Inhibitors

**eFigure 1. Meta-analysis on ASD and AD: First-Trimester Exposure**

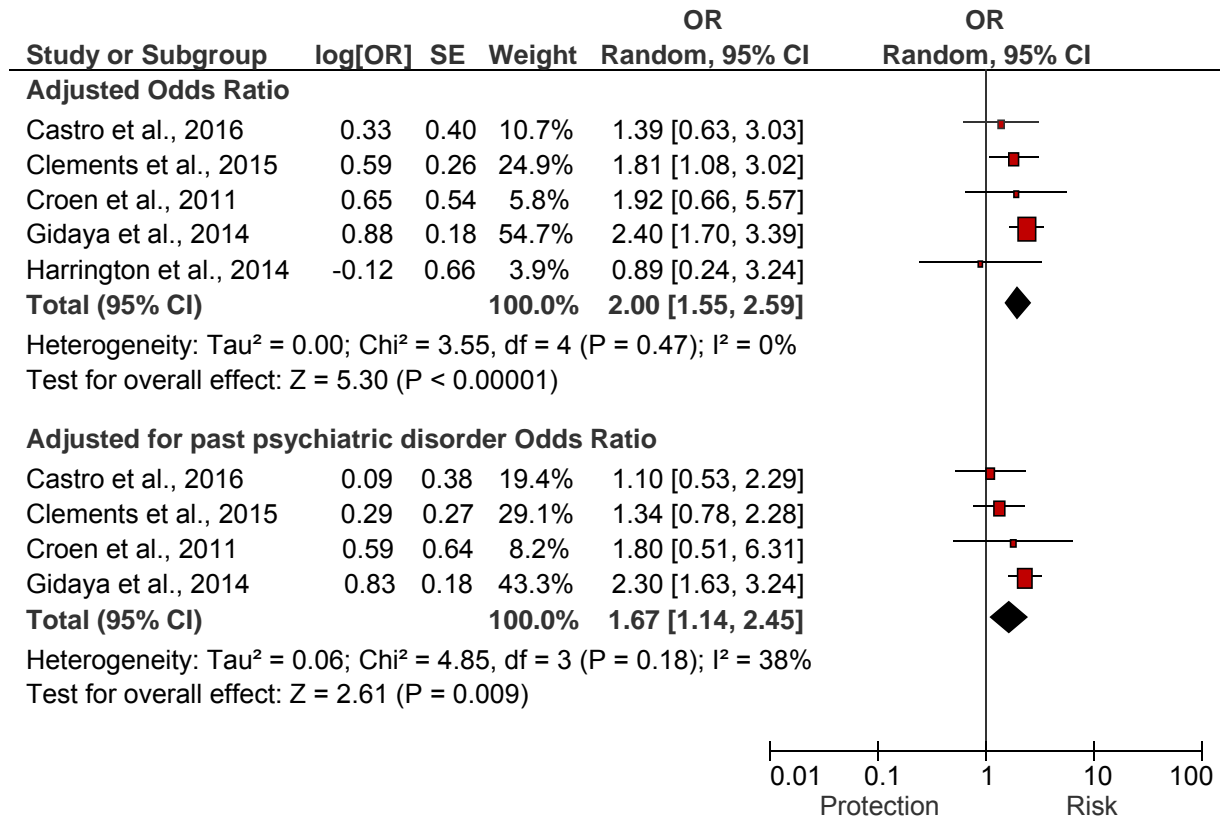


\* Adjusted for maternal depression, except for Rai et al. (any maternal psychiatric disorder)

For the forest plots, the log hazard or odds ratio and their standard error were calculated based on effect measures provided and their 95% confidence intervals. Some ORs reported in the table could slightly differ (centesimals) from published values due to the rounding of primary values.

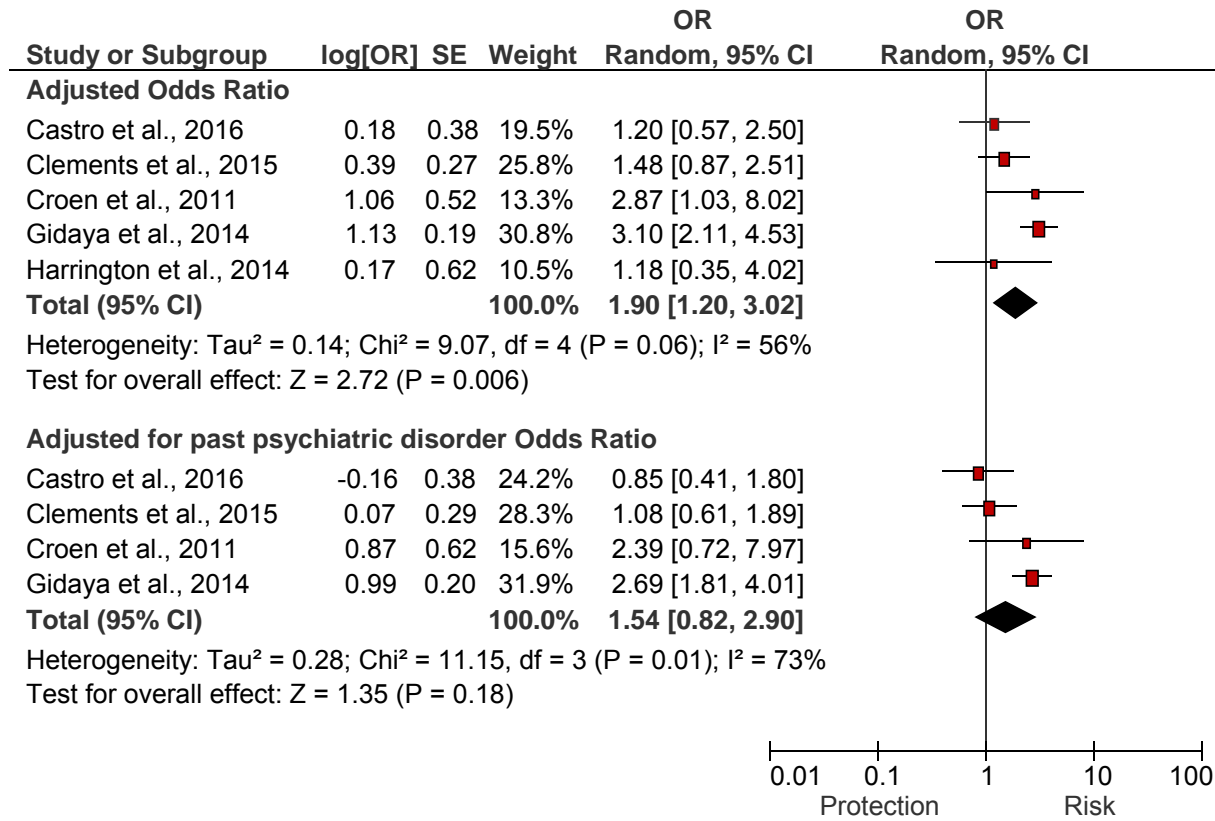


**eFigure 2.** Meta-analysis on ASD and AD: Second-Trimester Exposure



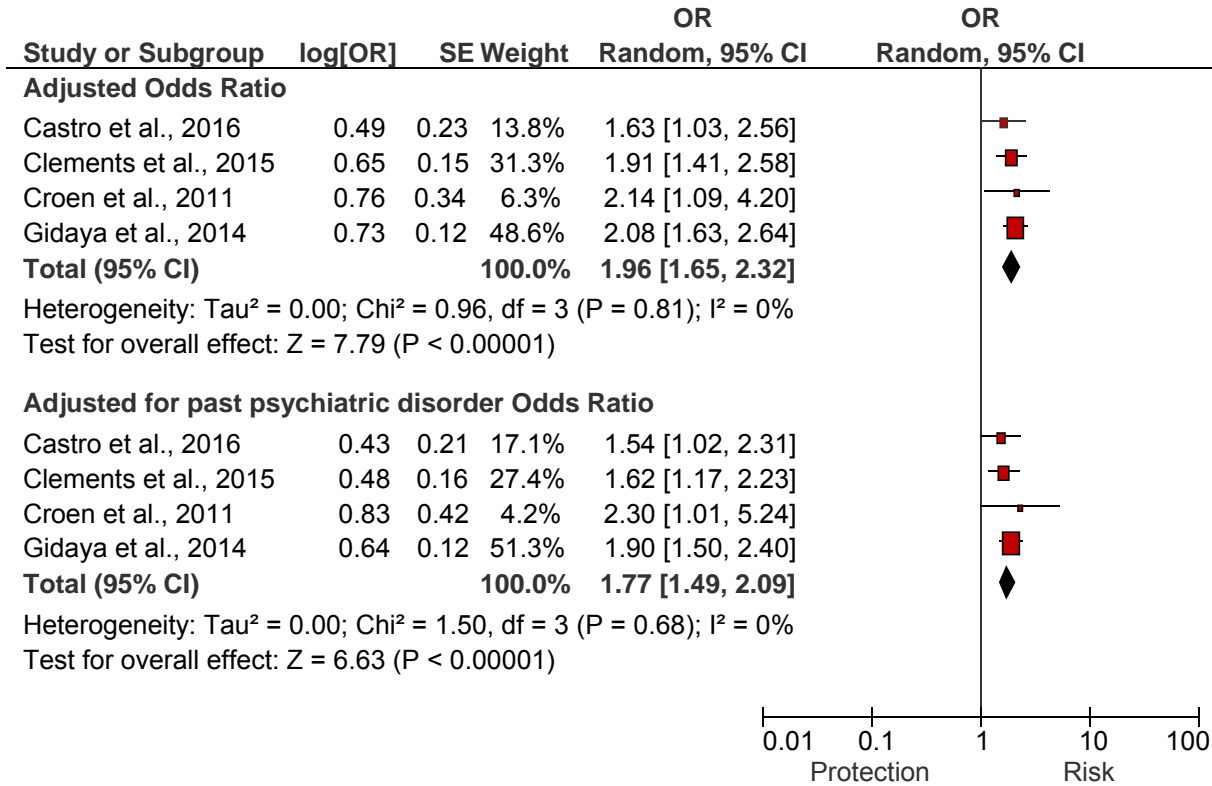
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**eFigure 3.** Meta-analysis on ASD and AD: Third-Trimester Exposure



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**eFigure 4. Meta-analysis on ASD and AD: Prepregnancy Exposure**



For the forest plots, the log hazard or odds ratio and their standard error were calculated based on effect measures provided and their 95% confidence intervals. Some ORs reported in the table could slightly differ (centesimals) from published values due to the rounding of primary values.