Supplementary Material

List of Supplementary Material for the article

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Supplementary tables for *Atomoxetine in early pregnancy and the prevalence of congenital malformations: A multinational study, Bröms et al.*

Supplementary Table 1. Codes used to determine exposure and outcome status			
	US MAX		Nordic countries
Codes used in outcome definition	**ICD-9**		**ICD-10**
Major congenital malformation	740-759		Q00.0 - Q89 Except: Q17.0, Q38.1, Q53, Q65.0-Q65.6, Q82.5, Q86.
Cardiac defects	745-747		Q20.0-Q26.4, Q26.8, Q26.9
Limb defects	754.5x, 755.x Except: 754.52, 754.53, 754.6x, 754.7x, 754.81, 754.82		Q66, Q68-Q74 Except: Q66.2-Q66.9, Q68.0, Q68.3-Q68.5
Chromosomal anomaly	758		Q90-99
Codes used in outcome definition	**ICD-9**	**CPT-4**	
Cardiac procedures and surgery codes	35.x, 36.x, 37.x (except 37.94), 38.x (except 38.18, 38.91, 38.92, 38.93, 38.94, 38.95, 38.98, 38.99), 39.x (except 39.27, 39.50, 39.95, 39.98)	00560, 00561, 00563, 33300-35190, 92992, 92993, 93530, 93531, 93532, 93533	
Codes used in exposure definition			**ATC**
Atomoxetine			N06BA09
Methylphenidate			N06BA04
Amphetamines			N06BA01-02, N06BA12

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Supplementary Table 2. Main differences in the design and analytic approaches used for the US and Nordic data.		
	US MAX cohort	**Nordic cohorts/countries**
Cohort	Live births	Live singleton births
Exclusions	Medications previously associated with teratogenic effects: Warfarin, ACE-inhibitors, antineoplastic drugs, colchicine, lithium, isotretinoin, misoprostol, thalidomide, valproic acid, carbamazepine	Gestational weeks ≤22 or >44 weeks
		Birth weight <300 g or >7000 g
Exposure window	First trimester: LMP to LMP + 90 days	First trimester: LMP to LMP + 97 days
Reference group	No exposure from 3 months before LMP to LMP + 90 days	No exposure from LMP to LMP + 97 days
Outcome assessment	First 3 months of life	First year of life, except first 3 months of life in Norway
Covariate assessment	ICD-9	ICD-10
	3 months before LMP to LMP + 90 days: Hypertension, diabetes, chronic renal disease, migraine/headache, sleep disorder/anxiety, delirium, depression, bipolar disorder, psychosis, schizophrenia, personality disorder, reaction to severe stress and adjustment disorders, anxiety, alcohol use disorder, other substance use disorder, epilepsy or convulsions	1 year before LMP to delivery, ICD-10: Hypertension O10, O16, I10-15, diabetes A10, chronic renal disease N00-19, N25-262, delirium, depression, bipolar disorder, psychosis, schizophrenia, personality disorder, reaction to severe stress and adjustment disorders, anxiety F40-48, except F43, alcohol use disorder Z71.4, O35.4, F10, other substance use disorder F11-19, Z71.5, Z86.4, epilepsy or convulsions G40
	3 months before LMP to LMP + 90 days: Number of distinct non-ADHD prescription drugs, number of physician visits, hospitalizations, number of distinct diagnoses, number of emergency visits, maternal comorbidity index	90 days before LMP to LMP + 97 days, ATC codes for non-ADHD drug prescriptions 1 year before LMP to LMP + 97 days, ICD-10 codes for hospitalizations, number of distinct main diagnoses
	ADHD	ADHD, ICD-10: F90
	Race/Ethnic group	Mothers' country of birth as recorded in birth register, (Nordic/non-Nordic)
	State of delivery	Country of delivery
	3 months before LMP to LMP + 90 days: Benzodiazepines, other hypnotics, barbiturates, anxiolytics, anticonvulsants, antidepressants, antipsychotics, antidiabetics/insulin, antihypertensives, opiods, methadone, buprenorphine, naltrexone, naloxone, triptans, NSAIDs	90 days before LMP to LMP + 97 days, ATC codes for concomitant drug use: migraine/headache N02C, sleep disorder/anxiety N05C, depression N06A, benzodiazepines, other hypnotics, barbiturates, anxiolytics, N05B, N05C, except N05CH (melatonin), anticonvulsants N03, antipsychotics N05A, antidiabetics/insulin A10, antihypertensives C02-04, C07-09, opioids N02A, methadone N07BC02, buprenorphine N07BC01,

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		naltrexone N07BB04, naloxone V03AB15, triptans N02C, NSAIDs M01A Potential teratogens: Danazol G03XA01, progestins G03D, methimazole, propylthiouracil H03BA, corticosteroids H02, fluconazole J02AC01 Medications previously associated with teratogenic effects: Warfarin B01AA03, ACE-inhibitors C09, antineoplastic drugs L01, colchicine M04AC01, lithium N05AN01, isotretinoin D05BB, misoprostol A02BB01, thalidomide L04AX02, valproic acid N03AG01, carbamazepine N03AF01
	3 months before LMP until LMP+90, date prescription was filled + duration of prescription. Potential teratogens: Danazol, progestins, methimazole, propylthiouracil, corticosteroids, fluxonazole	
	Obesity/overweight according to diagnostic codes, 3 months before LMP until LMP+90	Body mass index according to birth registers recorded at first antenatal visit, obesity BMI ≥30.0 kg/m^2
	Tobacco use according to diagnostic codes, 3 months before LMP until LMP+90	Smoking in the first trimester as recorded in the birth registers from first antenatal visit
	Preterm birth according to diagnostic codes	Preterm birth < 258 days, 37 weeks, as recorded in the birth registers Parity
Adjustment for confounding	Fine stratification on the propensity score	Fine stratification on the propensity score

ACE-inhibitors: Angiotensin converting enzyme inhibitors; ADHD: Attention deficit hyperactivity disorder; ATC: Anatomical Therapeutic Chemical Classification System; BMI: Body mass index; ICD: International Statistical Classification of Diseases and Related Health Problems; LMP: last menstrual period; NSAIDs: Non-steroidal anti-inflammatory drugs

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Supplementary table 3. Comparison of the risk of major malformations between infants born to women exposed to atomoxetine in early pregnancy and infants born to women without exposure to any ADHD drug. Sensitivity analysis changed exposure period †

Any major malformation

	Events in infants to women exposed to Atomoxetine N (per 1,000)	Events in infants to women without exposure N (per 1,000)	Crude PR (95% CI)	Adjusted PR (95% CI)
Nordic countries	22 (4.4)	89 005 (3.7)	1.20 (0.80 – 1.81)	1.00 (0.66 – 1.50)
US MAX	44 (4.9)	63 047 (3.5)	1.41 (1.05 – 1.87)	1.22 (0.92 – 1.63)
All countries	66 (4.7)	152 052 (3.6)	1.32 (1.04 – 1.67)	1.12 (0.89 – 1.42)

Cardiac malformations

Nordic countries	7 (1.4)	30 591 (1.3)	1.11 (0.53 – 2.32)	0.83 (0.40 – 1.73)
US MAX	24 (2.7)	22 583 (1.3)	2.14 (1.44 – 3.18)	1.90 (1.28 – 2.82)
All countries	31 (2.2)	53 174 (1.3)	1.77 (1.25 – 2.51)	1.43 (1.01 – 2.03)

Limb malformations

Nordic countries	6 (1.2)	9 627 (0.4)	3.02 (1.37 – 6.70)	2.48 (1.12 – 5.49)
US MAX	<11	11 481 (0.6)	0.18 (0.03 – 1.24)	0.17 (0.02 – 1.17)
All countries	7 (0.5)	21 108 (0.5)	1.01 (0.48 – 2.11)	0.86 (0.41 – 1.81)

†Nordic countries: Atomoxetine (LMP-30 days to LMP+97 days); US MAX: filled prescriptions with a days' supply overlapping with the first trimester
Numbers below 11 in the data from the US are not shown for integrity reasons.

ADHD: Attention deficit hyperactivity disorder
PR: prevalence ratio
MAX: Medicaid Analytic Extract
[a] A propensity score was obtained by fitting a logistic regression model that predicted the probability of exposure using the covariates listed in Supplementary table 2. Each country reported crude results as well as results by the propensity score-weighted individual strata to be pooled according to the Mantel-Haenszel method and presented as crude and adjusted PRs, respectively.