Selective serotonin reuptake inhibitors and venlafaxine in early pregnancy and risk of birth defects: population based cohort study and sibling design

Kari Furu,[1] Helle Kieler,[2] Bengt Haglund,[2] Anders Engeland,[1 3] Randi Selmer,[1] Olof Stephansson,[2 4] Unnur Anna Valdimarsdottir,[5 6] Helga Zoega,[5] Miia Artama,[7 8] Mika Gissler,[9 10] Heli Malm,[11 12] Mette Nørgaard[13]

EDITORIAL by Khalifeh and colleagues
RESEARCH, p 12

[1]Department of Pharmacoepidemiology, Division of Epidemiology, Norwegian Institute of Public Health, PB 4404 Nydalen, NO 0403 Oslo, Norway
[2]Department of Medicine Solna, Centre for Pharmacoepidemiology, Karolinska Institutet Stockholm, Sweden
[3]Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway
[4]Department of Women's and Children's Health, Division of Obstetrics and Gynecology, Karolinska Institutet, Stockholm, Sweden
[5]Centre of Public Health Sciences, Faculty of Medicine, School of Health Sciences, University of Iceland, Reykjavik, Iceland
[6]Department of Epidemiology, Harvard T.H.Chan School of Public Health, Boston, MA, USA
[7]Department of Medical Genetics, University of Helsinki, Helsinki, Finland
[8]Department of Child Psychiatry, University of Turku, Turku, Finland
[9]THL National Institute for Health and Welfare, Helsinki, Finland
[10]Nordic School of Public Health, Gothenburg, Sweden
[11]Teratology Information Service, HUSLAB and Helsinki University Central Hospital, Helsinki, Finland
[12]Department of Clinical Pharmacology, Helsinki University, Helsinki, Finland
[13]Department of Clinical Epidemiology, Institute of Clinical Medicine, Aarhus University Hospital, Aarhus, Denmark
Correspondence to: K Furu
kari.furu@fhi.no

Cite this as: *BMJ* 2015;350:h1798
doi: 10.1136/bmj.h1798

This is a summary of a paper that was published on thebmj.com as *BMJ* 2015;350:h1798

STUDY QUESTION

Does exposure to selective serotonin reuptake inhibitors (SSRIs) or venlafaxine in early pregnancy increase the risk of birth defects?

SUMMARY ANSWER

Covariate adjusted analyses in the full study cohort and the sibling controlled analyses point against a substantial teratogenic effect of SSRIs or venlafaxine.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

The teratogenicity of SSRIs and venlafaxine remains controversial. The general absence of strong associations between birth defects and SSRIs and venlafaxine diminishes concerns about teratogenicity.

Participants and setting

Nordic population (Denmark, Finland, Iceland, Norway, and Sweden) identified from nationwide health registers, 1996-2010. The full study cohort included women giving birth to 2.3 million live singletons. From this full cohort we identified a cohort of 2288 siblings.

Design, size, and duration

The full cohort comprised 36 772 infants exposed to SSRIs or venlafaxine during early pregnancy and 2 266 875 non-exposed infants. The sibling cohort comprised 980 infants exposed to SSRIs or venlafaxine during early pregnancy and 1308 non-exposed infants. In the full cohort we used logistic regression analyses to estimate odds ratios for birth defects according to exposure, with adjustment for potential confounders. To adjust further for potential confounding from familial factors, we carried out sibling controlled analyses (conditional logistic regression) including sibling pairs who were discordant for exposure to SSRIs or venlafaxine and birth defects.

Main results and the role of chance

Among 36 772 infants exposed to any SSRI in early pregnancy, 3.7% (n=1357) had a birth defect compared with 3.2% of 2 266 875 unexposed infants (covariate adjusted odds ratio 1.13, 95% confidence interval 1.06 to 1.20). In the sibling controlled analysis the adjusted odds ratio was 1.06 (0.91 to 1.24). The odds ratios for any cardiac birth defect with use of any SSRI or venlafaxine were 1.15 (95% confidence interval 1.05 to 1.26) in the covariate adjusted analysis and 0.92 (0.72 to 1.17) in the sibling controlled analysis. Exposure to any SSRI or venlafaxine increased the prevalence of right ventricular outflow tract obstruction defects (covariate adjusted odds ratio 1.48, 1.15 to 1.89); when restricted to the sibling cohort the adjusted odds ratio was 0.56 (0.21 to 1.49).

Bias, confounding, and other reasons for caution

Recall bias is avoided by using prospectively collected data from nationwide registers. We defined exposure to SSRIs or venlafaxine by dispensed drugs. Misclassification from women filling a prescription without taking the drug would if anything bias the effect estimates towards the null. We included smoking but were unable to include information on alcohol or other lifestyle factors. These may, however, be correlated with smoking, thus adjusting for smoking may at least have controlled for some of the effect. Still, it is likely that our estimates would have been even closer to 1.0 if we had been able to control better for lifestyle factors. This is corroborated by our findings in the sibling controlled analyses. However, owing to smaller sample size the sibling controlled analyses had lower statistical precision than the cohort study design. These births may also represent a selected part of the population.

Generalisability to other populations

This study was conducted in five countries, which increases its generalisability compared with carrying out a national study.

Study funding/potential competing interests

This study was funded by the authors' affiliations and the Swedish pharmacy company Apoteksbolaget. Apoteksbolaget had no role in the design and conduct of the study or the manuscript.

Selective serotonin reuptake inhibitors or venlafaxine in early pregnancy and birth defects. Odds ratios in unmatched and sibling controlled analyses

	Full cohort analyses		Sibling controlled analyses					
Type of birth defect	Crude odds ratio (95% CI) (n=2 303 647)	Adjusted* odds ratio (95% CI) (n=2 145 050)	No of families	No of infants	No exposed	No with birth defects	Crude odds ratio (95% CI)	Adjusted* odds ratio (95% CI)
Any	1.18 (1.12 to 1.24)	1.13 (1.05 to 1.20)	895	2288	980	923	1.04 (0.91 to 1.19)	1.06 (0.91 to 1.24)
Any cardiac	1.30 (1.20 to 1.42)	1.15 (1.05 to 1.26)	378	991	422	386	0.94 (0.76 to 1.16)	0.92 (0.72 to 1.17)
Right ventricular outflow tract obstruction	1.66 (1.32 to 2.10)	1.48 (1.15 to 1.89)	42	115	48	42	0.96 (0.51 to 1.81)	0.56 (0.21 to 1.49)

*Adjusted for maternal age, year of birth, birth order, smoking, maternal diabetes, country, and use of other prescribed drugs (antiepileptics (ATC code N03), anxiolytics and hypnotics (N05B and N05C), and angiotensin converting enzyme inhibitors (C09))

Antipsychotic drug use in pregnancy: high dimensional, propensity matched, population based cohort study

Simone N Vigod,[1 2 3] Tara Gomes,[2] Andrew S Wilton,[2] Valerie H Taylor,[1 3] Joel G Ray[2 4]

EDITORIAL by Khalifeh and colleagues
RESEARCH, p 12

[1]Women's College Research Institute; Department of Psychiatry, University of Toronto, Toronto, Ontario M5S 1B2, Canada
[2]Institute for Clinical Evaluative Sciences, Toronto, Ontario M4N 3M5
[3]Department of Psychiatry, Women's College Hospital; University of Toronto, Toronto, Ontario
[4]Departments of Medicine and Obstetrics and Gynaecology, St Michael's Hospital, University of Toronto, Toronto, Ontario M5B 1W8
Correspondence to: S N Vigod
simone.vigod@wchospital.ca

Cite this as: *BMJ* 2015;350:h2298
doi: 10.1136/bmj.h2298

This is a summary of a paper that was published on thebmj.com as *BMJ* 2015;350:h2298

thebmj.com
News: Extra £2m is needed to improve mental healthcare intelligence (*BMJ* 2015;350:h1140)

STUDY QUESTION

Does maternal use of antipsychotic medication during pregnancy affect important maternal medical outcomes (gestational diabetes mellitus, gestational hypertensive disorders and venous thromboembolism) and perinatal conditions (preterm birth and extremes of newborn weight)?

SUMMARY ANSWER

No, antipsychotic drug use in pregnancy did not substantially worsen the main maternal medical or short term perinatal outcomes in a cohort of women closely matched on baseline characteristics, but outcome event rates in this cohort were much higher than would be expected in the general population.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Limited studies evaluating atypical antipsychotic drugs in pregnancy suggested that these drugs were associated with increased risk for maternal metabolic complications in pregnancy, with resulting consequences. This larger study, which used high dimensional propensity score matching to minimise treatment selection bias, found that antipsychotic medication use in pregnancy had minimal evident impact on important maternal medical and short term perinatal outcomes.

Participants and setting

We considered all women who delivered a singleton infant between 2003 and 2012 in Ontario, Canada, and who were eligible for provincially funded drug coverage.

Main maternal and perinatal outcomes in matched cohort of 1021 women prescribed an antipsychotic drug during pregnancy and 1021 non-users

Outcome and use of antipsychotic medication	Matched cohort		
	No (%) with outcome	Relative risk (95% CI)	Adjusted relative risk (95% CI)*
Main maternal medical outcomes			
Gestational diabetes:			
Non-users	62 (6.1)	1.00 (referent)	1.00 (referent)
Antipsychotic users	71 (7.0)	1.15 (0.82 to 1.61)	1.10 (0.77 to 1.57)
Hypertensive disorders of pregnancy:			
Non-users	42 (4.1)	1.00 (referent)	1.00 (referent)
Antipsychotic users	48 (4.7)	1.14 (0.76 to 1.73)	1.12 (0.70 to 1.78)
Venous thromboembolism:			
Non-users	13 (1.3)	1.00 (referent)	1.00 (referent)
Antipsychotic users	12 (1.2)	0.92 (0.42 to 2.02)	0.95 (0.40 to 2.27)
Main perinatal outcomes			
Preterm birth (<37 weeks' gestation):			
Non-users	146 (14.3)	1.00 (referent)	1.00 (referent)
Antipsychotic users	148 (14.5)	1.01 (0.81 to 1.27)	0.99 (0.78 to 1.26)
Small for gestational age (birth weight <3rd centile):			
Non-users	51 (5.1)	1.00 (referent)	1.00 (referent)
Antipsychotic users	62 (6.1)	1.22 (0.84 to 1.77)	1.21 (0.81 to 1.82)
Large for gestational age (birth weight >97th centile):			
Non-users	23 (2.3)	1.00 (referent)	1.00 (referent)
Antipsychotic users	36 (3.6)	1.64 (0.96 to 2.78)	1.26 (0.69 to 2.29)

*Adjusted for a prescribed selective serotonin reuptake inhibitor (SSRI), non-SSRI, mood stabiliser, or benzodiazepine during the index pregnancy.

Design, size, and duration

With a high dimensional propensity score algorithm based on covariates derived from health administrative data, 1021 women using antipsychotic medication during pregnancy were matched 1:1 with 1021 non-users. Women with two or more consecutive prescriptions for an antipsychotic drug during pregnancy, at least one of which was filled in the first or second trimester, were considered antipsychotic users.

Main results and the role of chance

Compared with matched non-users, those prescribed an antipsychotic drug in pregnancy were not at higher risk of gestational diabetes (adjusted relative risk 1.10 (95% CI 0.77 to 1.57)), hypertensive disorders of pregnancy (1.12 (0.70 to 1.78)), or venous thromboembolism (0.95 (0.40 to 2.27)). The preterm birth rate, though high among antipsychotic users (14.5%) and matched non-users (14.3%), was not relatively different (adjusted relative risk 0.99 (0.78 to 1.26)). Neither birth weight <3rd centile nor >97th centile was associated with antipsychotic medication use in pregnancy (adjusted relative risks 1.21 (0.81 to 1.82) and 1.26 (0.69 to 2.29) respectively).

Bias, confounding, and other reasons for caution

The use of high dimensional propensity score matching is meant to minimise residual confounding and approximate relative risk estimates observed in a randomised clinical trial. Nonetheless, residual confounding may have persisted due to inadequate capture of variables such as smoking and obesity, or due to unmeasured factors such as psychiatric symptoms

Generalisability to other populations

We included only women for whom information on prescription medications was available through a provincially covered drug plan. Individuals eligible for this drug plan tend to have worse health states, greater disability, and lower socioeconomic status than individuals who pay privately for their medication. Although about 70% of women with serious mental illness receive coverage through this drug plan, these results may not be entirely generalisable to antipsychotic users who are more medically healthy and of higher socioeconomic status.

Study funding/potential competing interests

This study was supported by a grant from the Canadian Institutes of Health Research and by the Institute for Clinical Evaluative Sciences, which is funded by the Ontario Ministry of Health and Long-Term Care. Unrelated to this project, SNV received a consulting fee from Multidimensional Healthcare consulting, and VHT has received study funding from Bristol-Myers Squibb and has been a speaker for pharmaceutical companies.

Direct benefit of vaccinating boys along with girls against oncogenic human papillomavirus: bayesian evidence synthesis

Johannes A Bogaards,[1 2] Jacco Wallinga,[2] Ruud H Brakenhoff,[3] Chris J L M Meijer,[4] Johannes Berkhof[1]

EDITORIAL by Canfell

[1]Department of Epidemiology and Biostatistics, VU University Medical Centre, PO Box 7057, 1007 MB Amsterdam, The Netherlands
[2]Centre for Infectious Disease Control, National Institute for Public Health and the Environment, PO Box 1, 3720 BA Bilthoven, The Netherlands
[3]Department of Otolaryngology/Head and Neck Surgery, VU University Medical Centre, PO Box 7057, 1007 MB Amsterdam, The Netherlands
[4]Department of Pathology, VU University Medical Centre, PO Box 7057, 1007 MB Amsterdam, The Netherlands
Correspondence to: J A Bogaards
hans.bogaards@rivm.nl

Cite this as: *BMJ* 2015;350:h2016
doi: 10.1136/bmj.h2016

This is a summary of a paper that was published on thebmj.com as *BMJ* 2015;350:h2016

thebmj.com

- Clinical Review: Cancer vaccines (*BMJ* 2015;350:h988)
- Clinical Review: Developing role of HPV in cervical cancer prevention (*BMJ* 2013;347:f4781)
- Head To Head: Should boys receive the human papillomavirus vaccine? (*BMJ* 2009;339:b4928)

STUDY QUESTION

What would be the extent of the reduction in the burden of vaccine preventable cancer in men if boys were vaccinated along with girls against oncogenic human papillomavirus (HPV) types 16 and 18?

SUMMARY ANSWER

If boys are included in the current HPV immunisation programme in the Netherlands, about 110 boys would need to be vaccinated to gain one quality adjusted life year (QALY) and around 800 to prevent one cancer case.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Men benefit indirectly from vaccination of girls against HPV, but remain at risk of HPV associated cancers, especially anal cancer that occurs predominantly in men who have sex with men. Bayesian modelling enabled us to quantify the direct benefit of vaccinating boys by synthesising evidence from multiple sources, which could aid policy makers when deciding on HPV vaccination of boys.

Participants and setting

General population in the Netherlands. Data sources included cancer registry data, meta-analyses, and HPV typing studies.

Design, size, and duration

This study was a bayesian evidence synthesis of the incremental benefit of HPV vaccination of boys along with girls. We modelled the effect of including boys aged 12 into HPV vaccination programmes that currently target only girls, assuming that the reduced transmission of vaccine type HPV from vaccination of girls will lower the risk of HPV associated cancer in all men, but not the excess risk of HPV associated cancers among men who have sex with men. Data sources included cancer registry data, meta-analyses, and HPV typing studies.

Main results and the role of chance

Before HPV vaccination, 14.9 (95% credible interval 12.2 to 18.1) QALYs per 1000 men were lost to vaccine preventable HPV associated cancers in the Netherlands. This burden would reduce by 37% (28% to 48%) if the vaccine uptake among girls remains at the current level of 60% and by 66% (53% to 80%) if vaccine uptake among girls increases to 90%. We estimated the number of boys (posterior mean, 95% credible intervals) who would need to be vaccinated to prevent one additional cancer case among men, stratified by vaccine coverage among girls. If preadolescent girls continue to be vaccinated at the current uptake of 60% in the Netherlands, 795 (660 to 987) boys would need to be vaccinated to prevent one cancer case. This number increases to 1735 (1240 to 2900) if vaccine uptake among girls reaches the target of 90%. The incremental benefit of vaccinating boys when vaccine uptake among girls is high is driven by the prevention of anal carcinomas, which underscores the relevance of HPV prevention efforts for men who have sex with men.

Bias, confounding, and other reasons for caution

Our analysis concerns only the vaccination of preadolescent boys and does not consider targeted vaccination of men who have sex with men. In base case analyses, we considered only the direct benefit to the boy vaccinated, which does not depend on vaccine uptake in other boys. Numbers needed to vaccinate will be somewhat lower if one also considers the extra herd immunity in non-vaccinated men that results from vaccinating boys in addition to girls (figures are shown in sensitivity analyses).

Generalisability to other populations

Our results are likely to be generalisable to populations outside the Netherlands with similar incidences of HPV associated cancers and similar contributions of HPV types 16 and 18 to those cancers.

Study funding/potential competing interests

This study was supported by the EU Seventh Framework Programme of DG Research through the PREHDICT and COHEAHR projects, which received co-funding by the Health Research and Development Council of the Netherlands Organization for Scientific Research (ZonMW 121030032). JB has received fees for participation in expert meetings organised by GSK and Merck. CM has received fees for participation in expert meetings organised by Merck.

Numbers of boys who would need to be vaccinated (95% credible interval) to prevent outcomes related to HPV 16/18 infection in men

	Vaccine coverage among girls		
Outcome prevented	0%	60%	90%
Penile cancer	1595 (1314 to 2010)	3486 (2710 to 4650)	29 107 (16 828 to 79 557)
Anal cancer	1769 (1605 to 1954)	2162 (1810 to 2869)	2593 (1934 to 5129)
Oropharyngeal cancer	1048 (803 to 1441)	1975 (1405 to 2849)	6484 (3037 to 16 534)
Any cancer	466 (405 to 542)	795 (660 to 987)	1735 (1240 to 2900)

Autism phenotype versus registered diagnosis in Swedish children: prevalence trends over 10 years in general population samples

Sebastian Lundström,[1 2] Abraham Reichenberg,[3] Henrik Anckarsäter,[2] Paul Lichtenstein,[4] Christopher Gillberg[1]

[1]Gillberg Neuropsychiatry Centre, University of Gothenburg, Kungsgatan 12, 411 19, Gothenburg, Sweden
[2]Centre for Ethics, Law and Mental Health, University of Gothenburg, Sweden
[3]Departments of Psychiatry and Preventive Medicine, Mount Sinai School of Medicine, New York, NY, USA
[4]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden
Correspondence to: S Lundström
sebastian.lundstrom@gnc.gu.se

Cite this as: *BMJ* 2015;350:h1961
doi: 10.1136/bmj.h1961

This is a summary of a paper that was published on thebmj.com as *BMJ* 2015;350:h1961

thebmj.com
- Editorial: Is the prevalence of autism increasing in the United States? (*BMJ* 2014;348:g3088)
- Clinical Review: Developmental assessment of children (*BMJ* 2013;346:e8687)
- Practice: Recognising and diagnosing autism in children and young people: summary of NICE guidance (*BMJ* 2011;343:d6360)

STUDY QUESTION

What was the annual prevalence of the autism symptom phenotype (symptoms on which the diagnostic criteria are based) compared with national registered diagnoses for autism spectrum disorder in Swedish children born 1993-2002?

SUMMARY ANSWER

The annual prevalence of the autism spectrum disorder symptom phenotype was stable over the 10 year period in 9 and 12 year old children, whereas the annual prevalence of clinically diagnosed autism spectrum disorder in the service based national register steadily increased.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Numerous studies have suggested that the prevalence of autism spectrum disorder has increased substantially, and some recent studies have reported a population prevalence in excess of 2%. Our findings do not support a secular increase in the rate of the autism symptom phenotype.

Participants and setting

To estimate the prevalence of autism spectrum disorder we used data from the Child and Adolescent Twin Study in Sweden and the Swedish national patient register. From the twins study we included 19 993 (190 with autism spectrum disorder) twins born in the 10 year period from 1 January 1993 to 31 December 2002 whose parents had responded to the Autism-Tics, ADHD and other Comorbidities inventory, and from the register we included all children (n=1 078 975; 4620 with autism spectrum disorder) born in Sweden during 1993 to 2002.

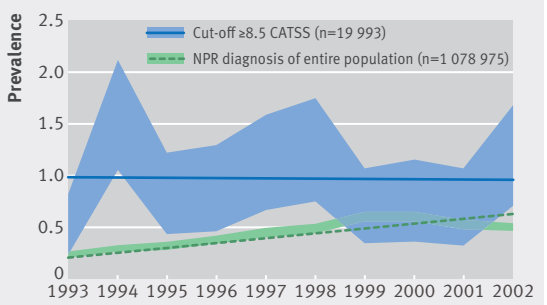
Design, size, and duration

Population based cohorts where the annual prevalence of autism spectrum disorder was monitored for 10 birth cohorts (1993-2002).

Main results and the role of chance

The annual prevalence of the autism symptom phenotype was stable during the 10 year period (P=0.87 for linear time trend). In contrast, there was a monotonic significant increase in prevalence of registered diagnoses of autism spectrum disorder in the national patient register (P<0.001 for linear trend). In the twin study the population prevalence of the autism symptom phenotype was 0.95% and the estimates for the 10 time points ranged from 0.52-1.59%, with overlapping confidence intervals at all time points (except 1993 *v* 1994). The effect of time was not significant (P=0.85 for test of time trend) and the regression analysis showed no effect of birth year (R^2=0.003, $F_{0.023}$, P=0.882). In the national patient register the population prevalence was 0.42% (n=4620) and the estimates ranged from 0.23-0.60%. There was an almost linear increase over the examined years (except for children born during 2000-02, where the follow-up was <10 years) and the test for time trend was significant (P<0.001). The effect of birth year was further supported by the results of the linear regression analysis (R^2=0.778, $F_{28.00}$, P=0.001).

Annual prevalence of autism spectrum disorder in Child and Adolescent Twin Study in Sweden (CATSS), national patient register (NPR), and NPR diagnoses in Swedish twins



Regression lines are depicted within 95% confidence intervals

Bias, confounding, and other reasons for caution

The Autism-Tics, ADHD and other Comorbidities inventory used for assessing the autism spectrum phenotype does not have perfect sensitivity or specificity, therefore some "diagnostic misclassification" should be expected. Differences in age and follow-up time should be taken into account in the comparison between the two samples. Parents of twins born during 1993-95 were interviewed when the twins were 12 years old, and children born during 2000-02 only had 7-9 years of follow-up. As a consequence there was a seeming decrease in the annual prevalence of autism spectrum disorder for those born during 2000-02.

Generalisability to other populations

We believe our findings are generalisable to other western countries.

Study funding/potential competing interests

The Child and Adolescent Twin Study in Sweden study was supported by the Swedish Council for Working Life, funds under the ALF agreement, the Söderström-Königska Foundation, and the Swedish Research Council (Medicine and SIMSAM). The funding sources had no role in the study design; collection, analysis, and interpretation of the data; or decision to submit this paper for publication. We have no competing interests.