



# First-trimester Exposure to Methylphenidate and risk of malformations: A Population-Based Cohort Study

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## Conflict of interest

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## Background

The use of methylphenidate (MPH) to treat attention deficit hyperactivity disorder has increased dramatically in western countries, and it is increasingly used by adults, including women of childbearing age. Very little is known about potential hazards of in utero exposure to MPH.

## Objective

We conducted this cohort study to estimate the risk of major congenital malformations following first trimester in utero exposure to MPH.

## Method

Data from 2005-2012 were extracted from the Danish National Patient Register, the Danish National Prescription Registry, the Medical Birth Registry and the Danish Civil Registration System. Exposure were defined as having redeemed of one or more prescriptions for MPH within a time window defined as 14 days before the beginning of the first trimester up to the end of the first trimester. Each exposed subject was matched on propensity score to 10 unexposed subjects with respect to maternal age, smoking status, body mass index, length of education, calendar year of completion of pregnancy, and concomitant use of antipsychotics, antidepressants, anxiolytics, and non-steroid anti-inflammatory drugs.

Table 1

Fetal outcomes and Prevalence Proportion Rates (PPR) comparing women taking methylphenidate to women not taking methylphenidate during first trimester, overall and by subgroup.

Sub-group	Exposed Events / no. pregnancies	Unexposed Events / no. pregnancies	PPR (95% CI)
All			
Major malformations	7 / 222	86 / 2,220	0.8 [0.3-1.8]
Cardiac malformations	3 / 222	32 / 2,220	0.9 [0.2-3.0]
Maternal age < 30			
Major malformations	6 / 161	63 / 1,637	1.0 [0.3-2.2]
Cardiac malformations	2 / 161	19 / 1,637	1.1 [0.1-4.4]
Maternal age ≥ 30			
Major malformations	1 / 61	23 / 583	0.4 [0.0-2.6]
Cardiac malformations	1 / 61	13 / 583	0.7 [0.0-4.9]
No use of confounding drugs <sup>a</sup>			
Major malformations	5 / 125	53 / 1,346	1.0 [0.3-2.5]
Cardiac malformations	3 / 125	17 / 1,346	1.9 [0.4-6.6]

a) Atomoxetine (ATC, N06BA09), Modafinil (N06BA07), Dexamphetamine (N06BA02), Antipsychotics (N05A), antidepressants (N06A), anxiolytics (N05B), and NSAIDs (M01A excluding M01AX).

## Results

We included 222 exposed and 2,220 unexposed pregnancies in the analysis. There was no statistically significant increase in major malformations (prevalence proportion rate 0.8; 95% CI: 0.3-1.8) or cardiac malformations (prevalence proportion rate 0.9; 95% CI: 0.2-3.0). Sensitivity analyses, using different definitions of exposure or previous users of MPH as a comparison, yielded comparable results.

## Conclusion

First trimester in utero exposure to methylphenidate does not appear to be associated with a substantially (i.e. more than two-fold) increased overall risk of major congenital malformations.

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