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Cardiac Malformation Risks Following Maternal First Trimester Methylphenidate Use

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Several studies have investigated congenital heart defect (CHD) risks following maternal first trimester (T1) methylphenidate use (tabulated review of the data available from the authors).¹⁻⁵

Although individually none of the studies provide clear evidence of an increased risk of CHD, a 2020 meta-analysis⁶ combining data from several studies^{1-3,5} described a small but statistically significant increased risk (RR = 1.59; 95% CI, 1.02 to 2.49). However, this meta-analysis only combined the crude counts of healthy and affected fetuses from the primary source studies while also including data from overlapping study samples (Pottegård et al,⁵ Källén et al,³ and Huybrechts et al² included; among other data, Huybrechts et al² included an update for the dataset previously described in the other two reports^{3,5}). Consequently, the pooled risk estimate did not consider the impact of measured confounders from the individual studies, and due to the overlapping datasets, the same case could have contributed to the analysis more than once.

The most recent study⁴ describes nearly 300 additional methylphenidate exposed pregnancies than previously reported from the same data source.² Although the study identified a non-statistically significant increased risk (aOR = 1.65; 95% CI, 0.89 to 3.05),⁴ understanding how this finding alters the interpretation of the available evidence as a whole remains difficult.

To provide clarity on CHD risks following in utero methylphenidate exposure, we combined the most recently published risk estimates from each available dataset using a meta-analysis approach.

Methods

A literature review of PubMed/MEDLINE/Embase was conducted in November 2022 searching databases from inception for studies (reviews and abstracts excluded) published in English describing T1 methylphenidate exposed and non-methylphenidate exposed comparator groups and fetal CHD outcomes.

Two authors (J.L.R., N.G.) independently reviewed the literature and extracted the data from studies meeting the inclusion criteria. Where available, adjusted point estimates and their confidence limits were extracted to include the least confounded point estimates. Where point estimates were unavailable, unadjusted odds ratios and confidence limits were calculated from crude CHD risks⁷ and Haldane-Anscombe correction was used in the case of zero events.⁸ Non-odds ratio point estimates were converted to odds ratios.⁹ Where datasets overlapped, data from the most recent publication (and hence the largest sample size) were included in the primary meta-analysis. A sensitivity analysis was performed, excluding unadjusted point estimates from the meta-analysis.

CHD risk estimates and their 95% confidence intervals were pooled in a fixed effects meta-analysis using the generic inverse variance method in RevMan 5.3.¹⁰ Heterogeneity was assessed using the I^2 statistic.

Results

Data were pooled from 7 study samples reported in 3 comparative cohort studies describing 4,015 T1 methylphenidate exposed and approximately 4.29 million non-exposed comparator pregnancies.^{1,2,4} The pooled odds ratio identified a small but statistically significant increased risk of CHD following T1 methylphenidate exposure (pooled OR = 1.32; 95% CI, 1.04 to 1.67; Figure 1). The sensitivity analysis did not reveal a substantially different risk estimate (pooled OR = 1.34; 95% CI, 1.05 to 1.70).

Discussion

These findings indicate that maternal T1 methylphenidate use may be associated with a small increased risk of CHD. Given that CHDs occur in approximately 1% of all live born infants,¹¹ the absolute risk following in utero methylphenidate exposure is estimated as 1.3%. This is equivalent to 3 additional infants with a CHD for every 1,000 exposed to methylphenidate.

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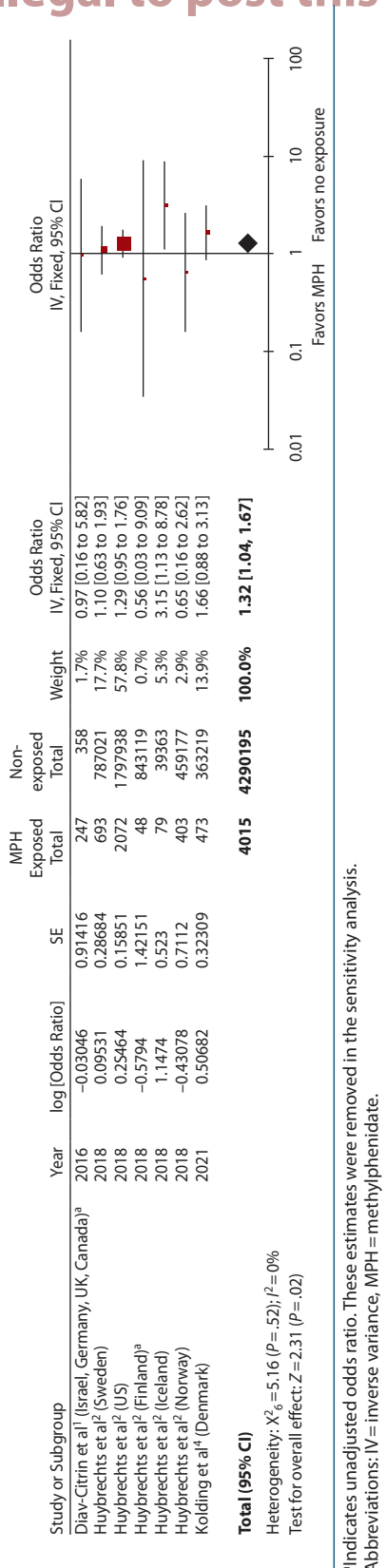
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Figure 1. Cardiac Malformation Risks Following Maternal Methylphenidate Use in the First Trimester



^aIndicates unadjusted odds ratio. These estimates were removed in the sensitivity analysis. Abbreviations: IV = inverse variance, MPH = methylphenidate.

As this small increased risk is demonstrated through the pooling of observational data, a causal association cannot be confirmed due to unmeasured confounding (eg, recreational drug or alcohol use) that may have influenced the primary source studies. However, maternal T1 methylphenidate use may be a prognostic risk factor for fetal CHD. Additional antenatal screening, with a fetal echocardiogram between 18–22 weeks gestation, could be considered following T1 methylphenidate exposure.

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