BENZODIAZEPINES EXPOSURE DURING PREGNANCY : A SYSTEMATIC REVIEW AND META-ANALYSIS OF OBSERVATIONNAL STUDIES

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AIM: to assess the risk of benzodiazepines exposure during pregnancy using a meta-analytical approach

Introduction

Benzodiazepines are widely used to treat diverse psychiatric diseases.

As in the general population, the use of benzodiazepines during pregnancy has increased sharply in recent years.

However, the safe use of benzodiazepines during pregnancy remains uncertain due to sometimes contradictory evidence

Methods:

- ✓ Systematic review and meta-analysis
- ✓ Search in Medline and Embase until February 2025
- ✓ Proprietary collaborative WEB-based meta-analysis platform: metaPreg.org (1)
- ✓ Random effects model
- ✓ Risk of bias: ROBINS-I tool (2)

Inclusion criteria:

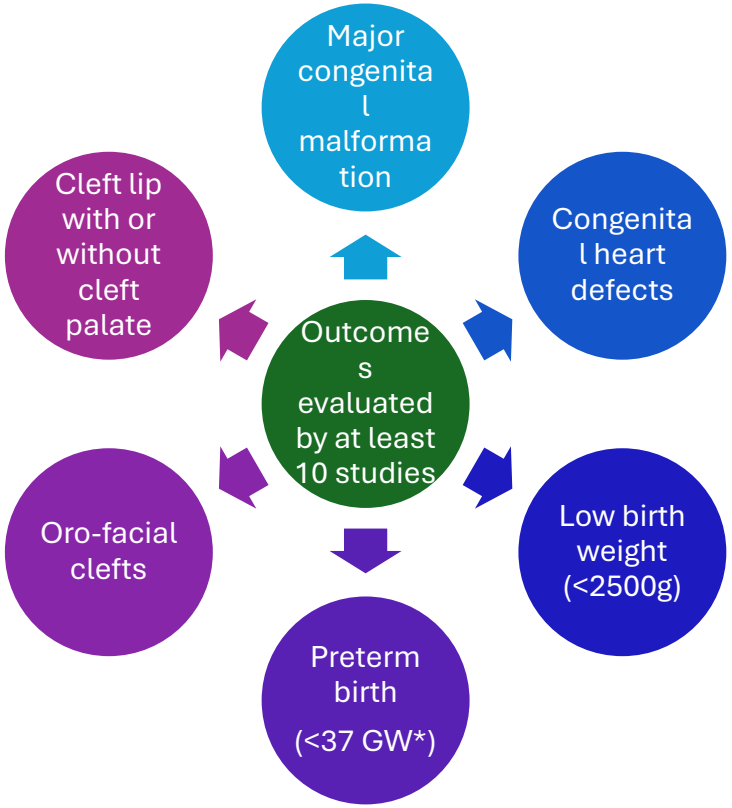
- ✓ Observational studies with non-exposed comparator group (sick or disease free)

Exclusion criteria:

- ✓ Studies assessing benzodiazepines in epilepsy only

References:
(1) metaPreg - Medicines during Pregnancy: Meta-analysis and knowledge base. Available on: http://metapreg.org/
(2) Sterne. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ.2016;355.

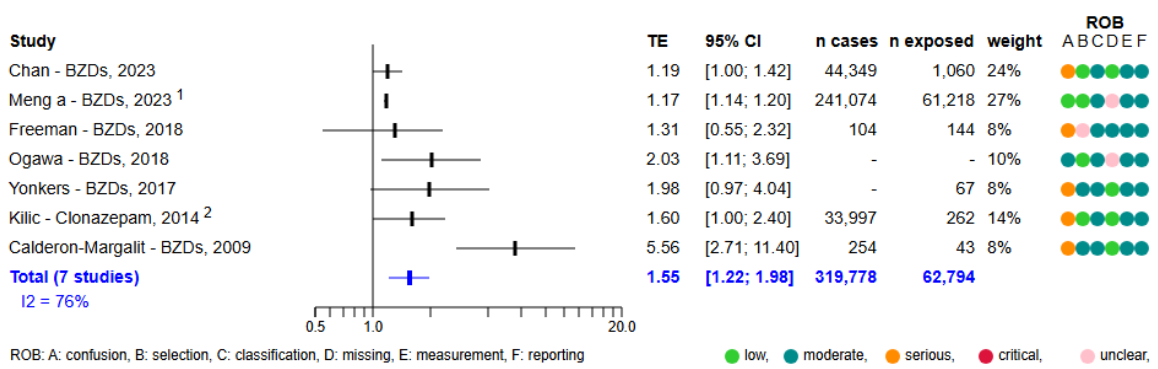
Results

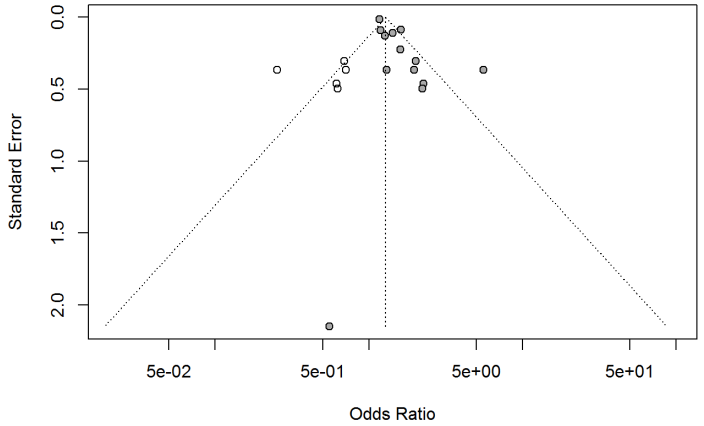


	Major congenital malformation (MCM)	Cleft lip with or wihout cleft palate	Congenital heart defects	Oro-facial clefts	Preterm birth (<37 GW*)	Low birth weight (LBW) (<2500g)
Main analysis	**OR = 1.12 [1.04, 1.21]; k=14; I2=45%; N exposed> 91280**	**OR = 2.00 [1.32, 3.03]; k=11; I2=60%; N exposed> 1234**	**OR = 1.15 [1.03, 1.28]; k=11; I2=47%; N exposed> 90894**	**OR = 1.32 [0.97, 1.80]; k=10; I2=55%; N exposed> 96699**	**OR = 1.51 [1.29;1.77]]; k=13; I2=74%; N exposed> 66,644**	**OR = 1.95 [1.44, 2.65]; k=12 ; I2=78%; N exposed> 2924**
Sensitivity analysis excluding studies with critical risk of confusion bias	**OR = 1.07 [1.01, 1.13]; k=4; I2=40%; N exposed = 86972**	OR = 0.80 [0.40, 1.70]; k=1; N exposed = 64	OR = 1.10 [0.99, 1.22]; k=3; I2=70%; N exposed = 86816	OR = 1.03 [0.78, 1.34]; k=2; I2=54%; N exposed = 91118	**OR= 1.55 [1.22, 1.98]; k=7; I2=76%; N exposed> 62794**	**OR = 2.17 [1.06, 4,51]; k=6; I2=89%; N exposed> 1331**
Publication bias	Low p=0.4	probable (p=0.1) **Trim and Fill OR = 1.29 [1.07; 1.54]; k = 17 (5 added studies)**	Low p=0.25	Low p=0.36	Critical, p=0.004 **Trim and Fiil : OR=1.29 [1.09; 1.52]; k = 18 (5 added studies)**	Low p=0.18

Sensitivity analysis : excluding studies with critical risk of confusion

PRETERM (<37GW)

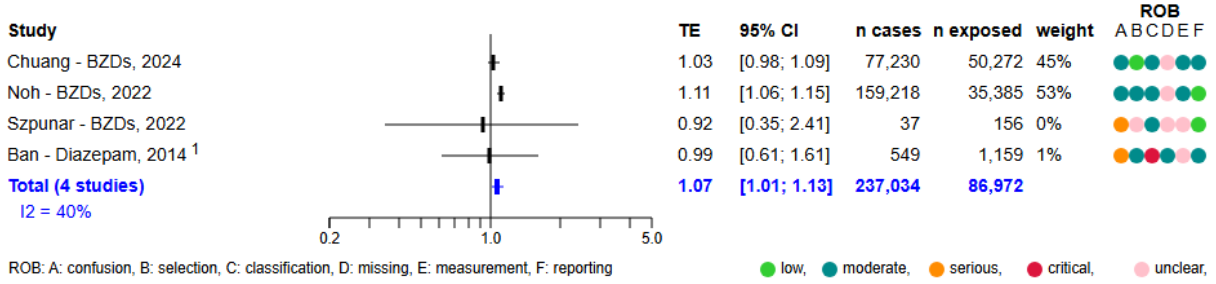




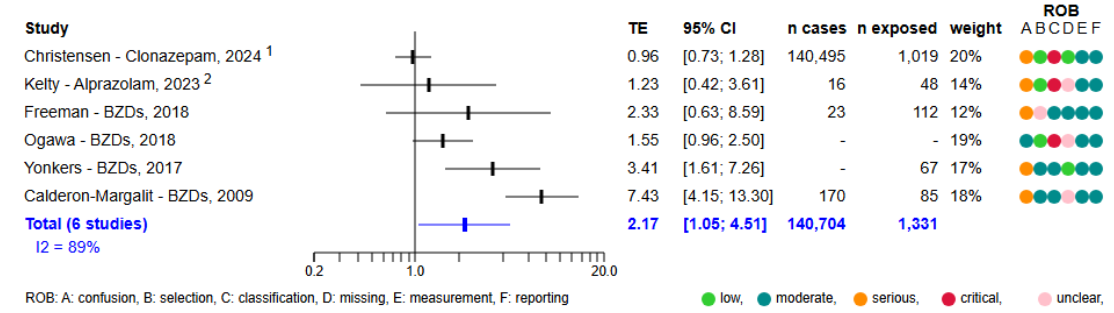
OR = 1.29 [1.07; 1.54] ;
k = 17 (5 added studies)

Trim-and-fill method

MAJOR CONGENITAL MALFORMATIONS



LOW BIRTH WEIGHT (<2500G)



CONCLUSIONS

The data on exposure to benzodiazepines currently available do not allow us to conclude on their safety during pregnancy.

RECOMMENDATIONS

Further high-quality studies controlling for important confounding factors are still needed.