

The prevalence of genomic anomalies by onset and severity of isolated fetal growth restriction: a systematic review and meta-analysis

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OBJECTIVES

Genetic causes underlie a considerable proportion of fetal growth restriction (FGR) cases, even in the absence of prenatally diagnosed major fetal structural anomalies. Past meta-analyses have shown that a conventional **karyotype** can detect chromosomal abnormalities in 6% of **apparently isolated FGR cases (iFGR)** and chromosomal microarray (**CMA**) analysis can additionally detect submicroscopic structural chorosomal anomalies in 4% of these cases. The introduction of prenatal **exome sequencing** indicated that, even with a normal karyotype, apparently iFGR fetuses may have a risk of monogenic disorders as high as 12%.

The aim of this systematic review and meta-analysis is to critically appraise the literature and synthesize the evidence on genomic abnormalities in iFGR, according to gestational age at onset and disease severity.

METHODOLOGY

- Open Science Framework registered protocol [*10.17605/OSF.IO/VJMDZ*]
 - Inception – June 2026
 - Newcastle-Ottawa Scale (NOS) for risk of bias
 - PRISMA guideline
 - Generalized linear mixed models (GLMM) [*metaprop* in R] for pooled event proportions
- Observational studies reporting **genomic anomalies** in **iFGR** cases detected by

Karyotype

CMA

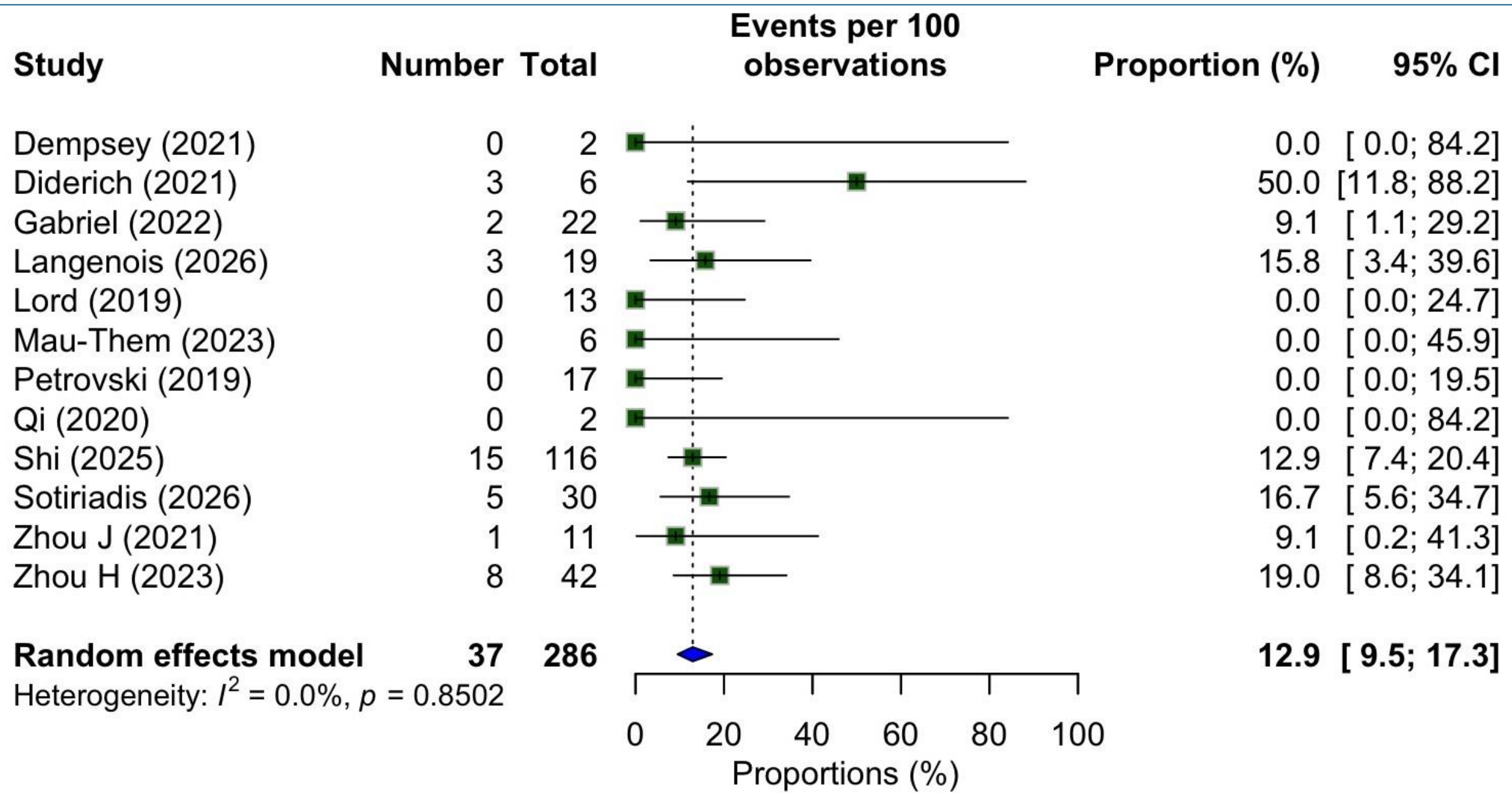
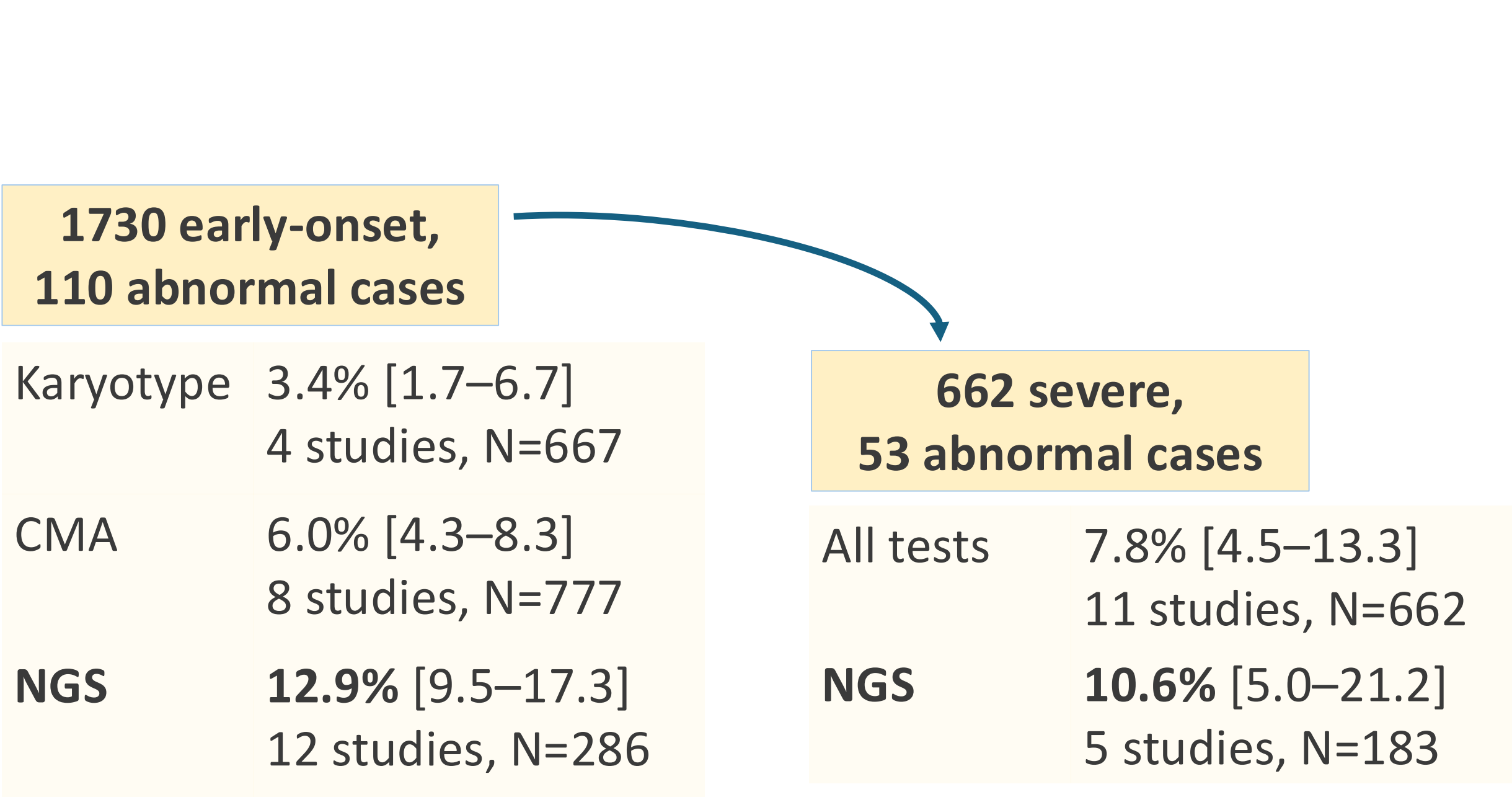
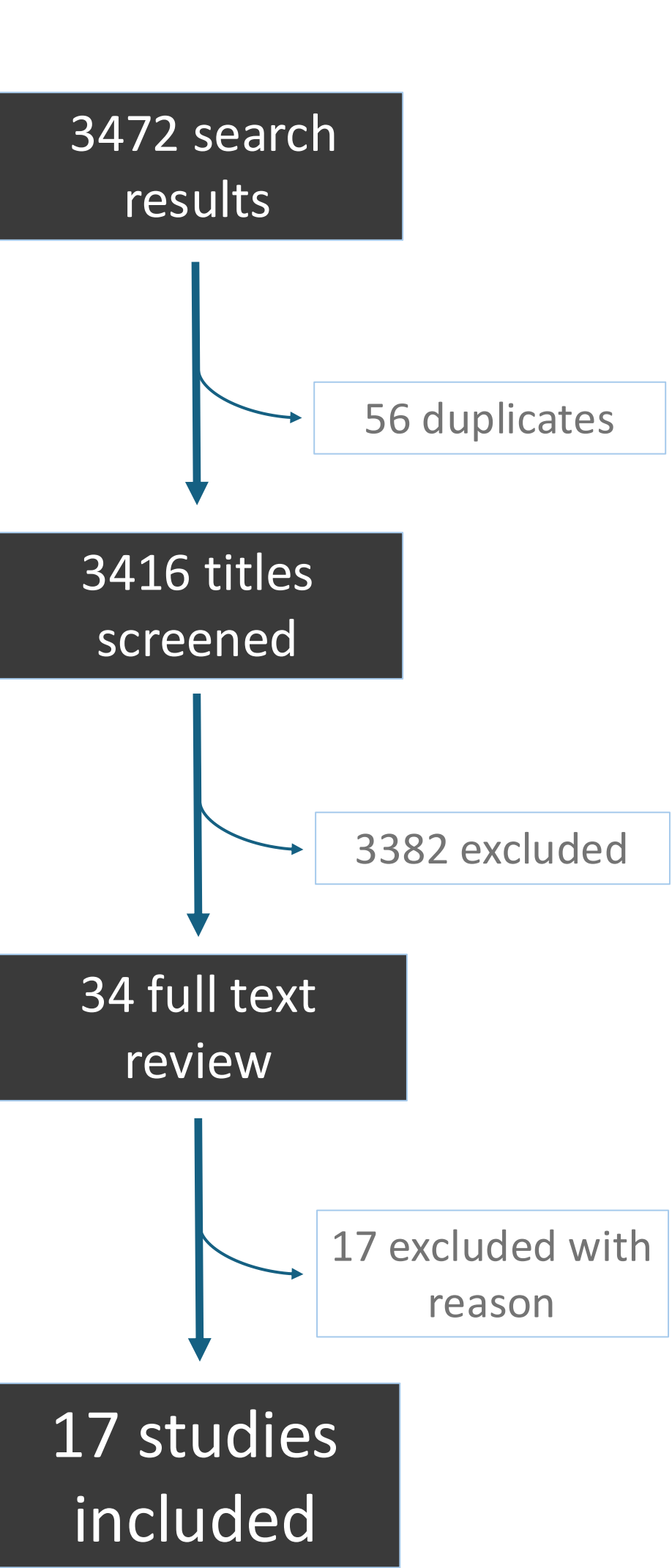
NGS
 - iFGR was defined in the **absence of prenatally identified major structural anomalies**
- According to **gestational age at onset**, FGR was defined as

late-onset (>32 weeks)

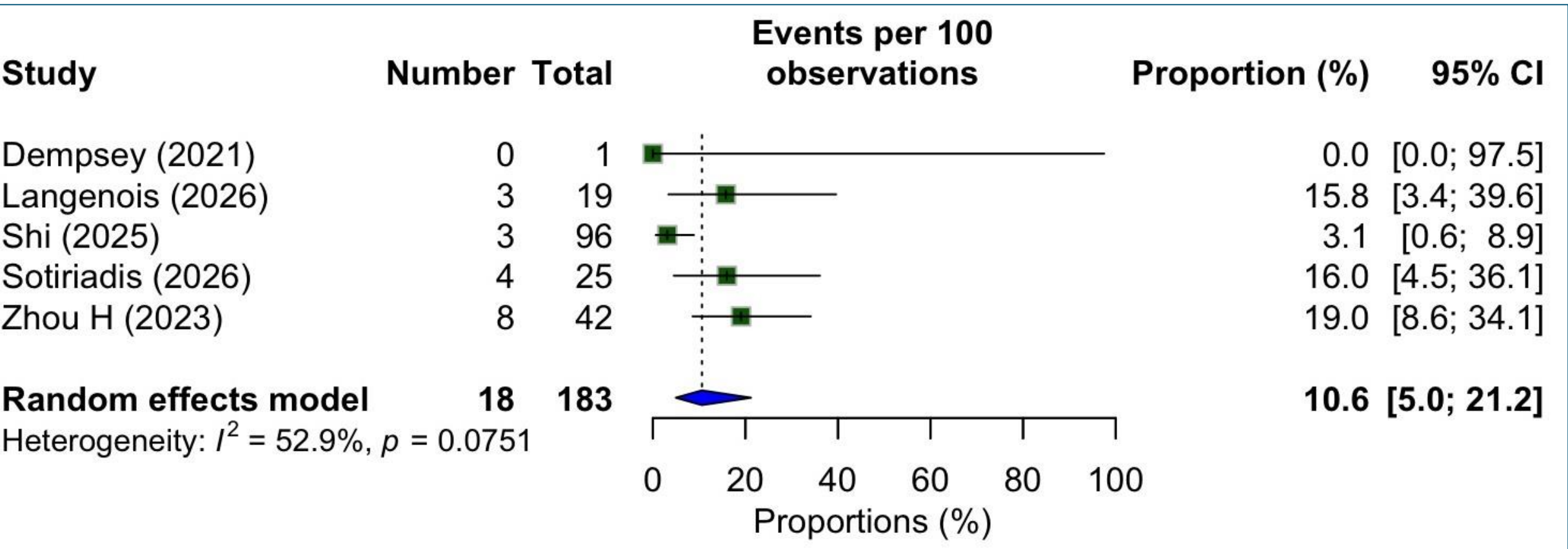
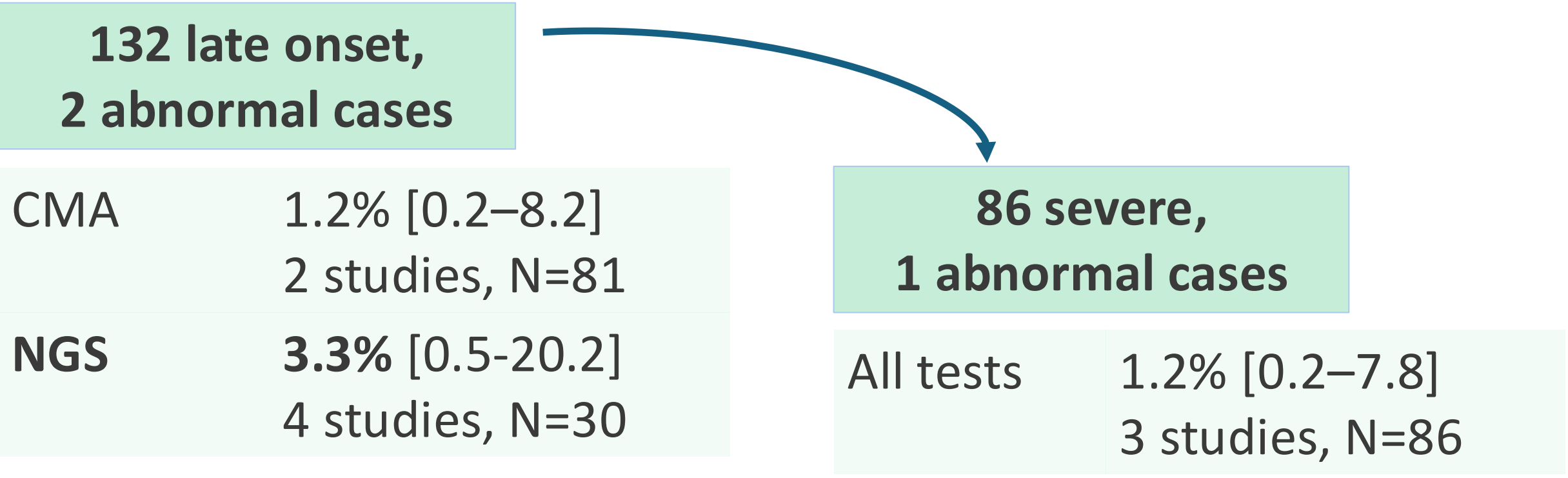
early-onset (<32 weeks)

very early-onset (<28 weeks)
 - Severe** FGR was defined as **EFW or AC below the 3rd percentile**

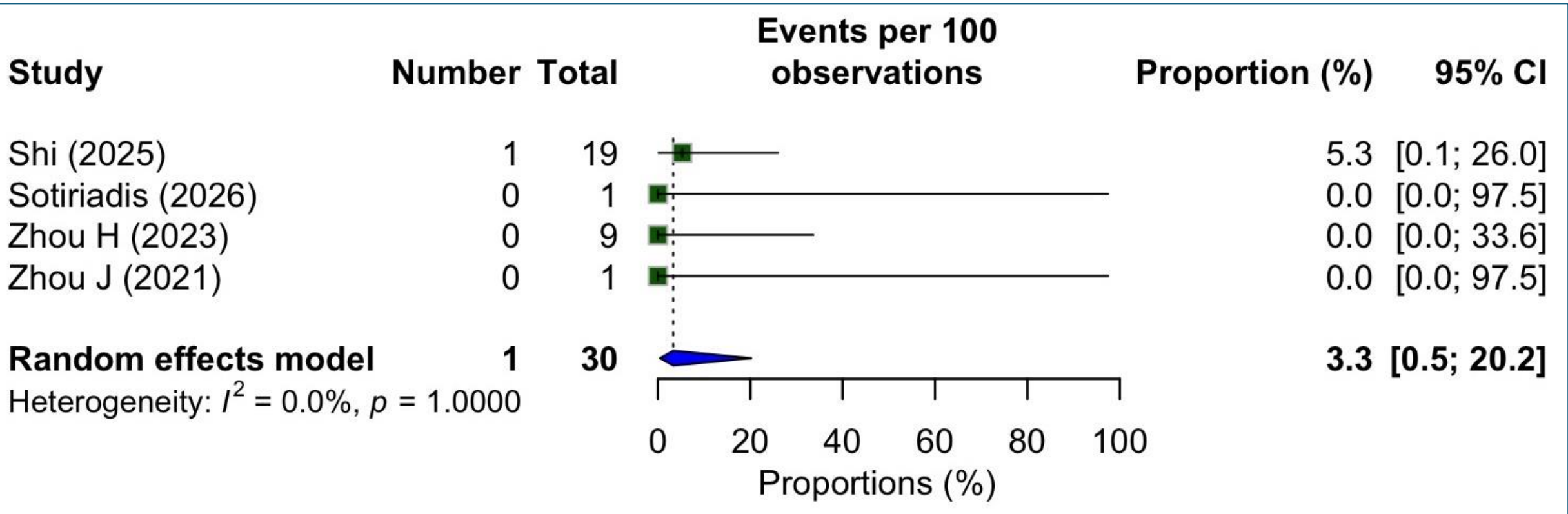
RESULTS



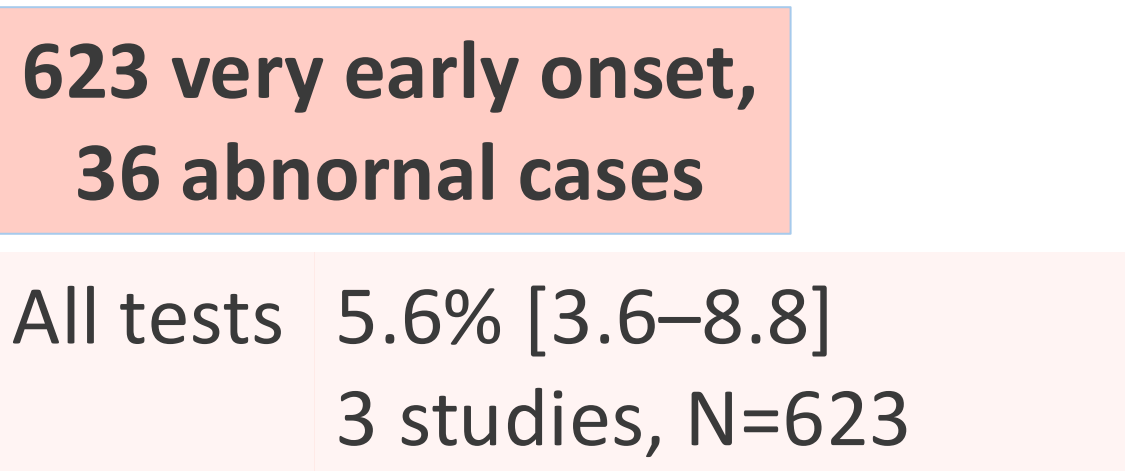
Forest plot of pooled proportions of the diagnostic yield of NGS in early-onset iFGR.



Forest plot of pooled proportions of the diagnostic yield of NGS in early-onset and severe iFGR.



Forest plot of pooled proportions of the diagnostic yield of NGS in late-onset iFGR.



LIMITATIONS

- Insufficient evidence to perform the predefined secondary analyses for
 - very early and severe iFGR
 - subgroups according to the 2016 Delphi criteria definition of FGR
 - confirmed postnatal phenotype
- FGR not homogenously defined, also isolated FGR; some cohorts including cases with evidence of placental insufficiency, others with soft markers or postnatal identification of a missed structural abnormality
- Timing of genomic test might differ from the time of FGR onset

CONCLUSION

- The likelihood of detecting a genomic abnormality is higher in early-onset and severe iFGR
- NGS showed the highest diagnostic yield, reaching approximately 13% in early-onset iFGR and 3% in late-onset iFGR
- Further research is needed to establish a uniform classification of FGR and to generate larger studies with postnatal confirmation of findings

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