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Prenatal MRI biomarkers and neurodevelopmental outcomes in fetal brain abnormalities: a systematic review, evidence map, and ventriculomegaly-focused meta-analysis

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ADMINISTRATIVE INFORMATION

Support - This review has not received any specific funding.

Review Stage at time of this submission - Preliminary searches.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 30 April 2026 and was last updated on 5 May 2026.

INTRODUCTION

Review question / Objective This systematic review aims to evaluate whether prenatal magnetic resonance imaging (MRI) findings or MRI-derived biomarkers are associated with postnatal neurodevelopmental or neurologic outcomes in fetuses with suspected or confirmed brain abnormalities.

The review question is: In fetuses undergoing prenatal MRI for suspected or confirmed brain abnormalities, which qualitative MRI findings, MRI-detected associated abnormalities, severity categories, isolated or non-isolated status, or quantitative MRI-derived biomarkers are associated with adverse postnatal neurodevelopmental or neurologic outcomes?

Because eligible studies are expected to vary substantially in fetal condition, MRI biomarker definition, follow-up duration, and outcome assessment, the review will present an evidence map of prenatal MRI biomarker readiness. Quantitative synthesis will be performed only for biomarker-outcome pairs with sufficiently comparable data. Based on full-text verification, ventriculomegaly is anticipated to be the primary condition category suitable for quantitative synthesis.

Rationale Fetal brain MRI is increasingly used after prenatal ultrasound to characterize suspected fetal brain abnormalities and to support prenatal counseling. Although MRI can improve anatomical assessment and reveal additional abnormalities not detected by ultrasound, its value for predicting postnatal neurodevelopmental outcomes remains uncertain.

For families and clinicians, the most important question is often not only whether a fetal brain abnormality is present, but whether the abnormality is likely to result in adverse neurodevelopment after birth. Existing studies have reported associations between specific prenatal MRI findings and later outcomes, including ventriculomegaly, corpus callosum

abnormalities, posterior fossa abnormalities, cortical developmental malformations, cerebellar abnormalities , and non-isolatedbrain abnormali tie s. However, the evidence is heterogeneous because of differences in MRI timing, abnormality classification, follow-up duration, neurodevelopmental assessment tools,
and outcome definitions.

A systematic review and meta-analysis is therefore needed to synthesize the available evidence, identify prenatal MRI biomarkers associated with adverse postnatal neurodevelopmental outcomes, and evaluate their potential role in prenatal counseling, postnatal risk stratification, and early intervention planning.

During full-text verification, we found that many prenatal MRI biomarker studies reported diagnostic, biometric, or imaging follow-up outcomes without extractable standardized postnatal neurodevelopmental data. Therefore, the synthesis strategy was refined to distinguish between biomarkers that are meta-analysis ready, biomarkers supported by prognostic accuracy or small cohort evidence, and biomarkers that remain diagnostic, biometric, secondary, or narrative.

This refinement is intended to improve transparency and avoid inappropriate pooling of heterogeneous outcomes, such as termination of pregnancy, perinatal death, postnatal imaging abnormalities, and child neurodevelopmental outcomes.

Condition being studied Fetal brain abnormalities assessed by prenatal magnetic resonance imaging. These abnormalities include, but are not limited to, ventriculomegaly, corpus callosum abnormalities, posterior fossa abnormalities, cerebellar abnormalities, cortical developmental malformations, midline brain abnormalities, and fetal brain parenchymal abnormalities. These conditions are clinically important because they may be associated with variable postnatal neurodevelopmental outcomes, ranging from normal development to cognitive impairment, motor delay, language delay, epilepsy, cerebral palsy, or other neurological abnormalities. Prenatal MRI is increasingly used to refine the anatomical diagnosis after ultrasound and may provide prognostic information for prenatal counseling and postnatal follow-up planning.

METHODS

Search strategy We will search MEDLINE/ PubMed, Embase, Web of Science, Scopus, Cochrane Library, and ClinicalTrials.gov from database inception to the final search date. Reference lists of included studies and relevant reviews will also be screened manually. No language restriction will be applied during the database search.

The preliminary PubMed search strategy will be:

((fetal[Title/Abstract] OR foetal[Title/Abstract] OR prenatal[Title/Abstract] OR antenatal[Title/Abstract] OR "in utero"[Title/Abstract])
AND
("magnetic resonance imaging"[Title/Abstract] OR MRI[Title/Abstract] OR "MR imaging"[Title/ Abstract])
AND
(brain[Title/Abstract] OR cerebral[Title/Abstract] OR ventriculomegaly[Title/Abstract] OR "corpus callosum"[Title/Abstract] OR "posterior fossa"[Title/Abstract] OR cerebellum[Title/Abstract] OR cortical[Title/Abstract] OR sulcation[Title/ Abstract] OR "brain abnormality"[Title/Abstract])
AND
(neurodevelopment*[Title/Abstract] OR developmental[Title/Abstract] OR postnatal[Title/ Abstract] OR cognitive[Title/Abstract] OR motor[Title/Abstract] OR language[Title/Abstract] OR epilepsy[Title/Abstract] OR "cerebral palsy"[Title/Abstract] OR outcome*[Title/Abstract]))

The search strategy will be adapted for each database using appropriate controlled vocabulary and syntax.

Participant or population The population will include fetuses who underwent prenatal brain MRI because of suspected or confirmed fetal brain abnormalities and who had postnatal neurodevelopmental, neurological, clinical, or imaging follow-up. Eligible fetal brain abnormalities may include ventriculomegaly, corpus callosum abnormalities, posterior fossa abnormalities, cerebellar abnormalities, cortical developmental malformations, midline brain abnormalities, and brain parenchymal abnormalities. Studies including singleton or multiple pregnancies will be eligible if data for fetuses with prenatal MRI and postnatal outcome assessment can be extracted. Studies limited to postnatal MRI without prenatal MRI data will be excluded.

Intervention No therapeutic intervention will be evaluated in this review. The index factors of interest are prenatal MRI biomarkers and MRI findings used for prognostic assessment. These may include qualitative MRI findings, MRI-detected additional abnormalities, isolated versus non-

isolated fetal brain abnormalities, severity grading of abnormalities, and quantitative MRI-derived markers such as ventricular size, brain volume, cerebellar measurements, corpus callosum measurements, cortical development, sulcation markers, diffusion-related metrics, or other MRI biomarkers reported by the included studies.

Comparator Comparators may include fetuses without the MRI biomarker of interest, fetuses with normal or less severe MRI findings, isolated versus non-isolated fetal brain abnormalities, different severity categories of the same abnormality, or ultrasound findings when available. For studies without an explicit comparator group, prognostic associations between prenatal MRI findings and postnatal outcomes will be extracted and synthesized when possible.

Study designs to be included We will include cohort studies, case-control studies, longitudinal clinical-imaging studies, prognostic factor studies, prediction model studies, and diagnostic/prognostic accuracy studies if they evaluate prenatal MRI findings or MRI-derived biomarkers in relation to postnatal neurodevelopmental, neurologic, or clinically relevant outcome data.

Small case series may be included in the evidence map or narrative synthesis if they provide clinically relevant fetal MRI and postnatal outcome information, but they will not be included in quantitative meta-analysis unless they provide extractable denominators and outcome events. Single case reports, editorials, guidelines, reviews, non-human studies, and conference abstracts without sufficient original data will be excluded from quantitative synthesis.

Eligibility criteria Studies will be eligible if they meet the following criteria:

1. include fetuses who underwent prenatal brain MRI for suspected or confirmed fetal brain abnormalities;

2. report at least one prenatal MRI finding, MRI-derived measurement, or MRI biomarker;

3. provide postnatal neurodevelopmental, neurological, clinical, or imaging follow-up; and

4. report sufficient data to extract or calculate outcome frequencies, effect estimates, diagnostic/prognostic accuracy measures, or associations between MRI findings and postnatal outcomes.

Eligible fetal brain abnormalities may include ventriculomegaly, corpus callosum abnormalities, posterior fossa abnormalities, cerebellar abnormalities, cortical developmental malformations, midline brain abnormalities, and fetal brain parenchymal abnormalities.

Exclusion criteria will include case reports, narrative reviews, editorials, commentaries, conference abstracts without full data, animal studies, phantom studies, purely technical MRI studies without postnatal outcome data, studies limited to postnatal MRI without prenatal MRI findings, and studies reporting only pregnancy termination, stillbirth, or perinatal mortality without neurodevelopmental or neurological outcome assessment.

For the main quantitative synthesis, studies must provide extractable child-level or cohort-level outcome data, including numerators and denominators or compatible effect estimates for prenatal MRI biomarker-outcome associations. Outcomes will be prioritized in the following order: standardized neurodevelopmental assessment, neurologic clinical outcome, epilepsy, cerebral palsy, motor/cognitive/language impairment, abnormal neurologic examination, and clinically significant developmental delay.

Pregnancy termination, fetal death, neonatal death, and postnatal imaging abnormalities will be recorded separately and will not be combined with child neurodevelopmental outcomes unless the original study explicitly defines and reports a composite outcome and the composite is analyzed separately.

Information sources The following electronic databases will be searched from inception to the final search date: MEDLINE/PubMed, Embase, Web of Science, Scopus, Cochrane Library, and ClinicalTrials.gov. Reference lists of included studies and relevant reviews will also be manually screened to identify additional eligible studies. Grey literature and trial or study registries will be considered when relevant. If important data are missing or unclear, study authors may be contacted for additional information. No language restriction will be applied during the database search, and non-English studies will be translated when feasible.

Main outcome(s) The primary outcome will be adverse postnatal neurodevelopmental outcome after prenatal MRI assessment of fetal brain abnormalities. Adverse neurodevelopmental outcome will include developmental delay, cognitive impairment, motor impairment, language

delay, epilepsy, cerebral palsy, abnormal standardized developmental assessment scores, or clinically significant neurological abnormalities during postnatal follow-up. When available, outcomes assessed at 12 months or later will be prioritized. Effect measures may include odds ratios, risk ratios, hazard ratios, proportions, sensitivity, specificity, or other reported measures of association between prenatal MRI biomarkers and postnatal outcomes.

Additional outcome(s) Secondary outcomes will include disease-specific rates of adverse neurodevelopmental outcome, outcome differences between isolated and non-isolated fetal brain abnormalities, prognostic value of MRI-detected additional abnormalities, associations between abnormality severity and outcome, and postnatal imaging abnormalities related to prenatal MRI findings. Additional analyses may include outcomes according to abnormality type, such as ventriculomegaly, corpus callosum abnormalities, posterior fossa abnormalities, cerebellar abnormalities, cortical developmental malformations, midline abnormalities, or fetal brain parenchymal abnormalities.

Data management All records identified from electronic databases will be imported into reference management software and duplicate records will be removed. Two reviewers will independently screen titles and abstracts, assess full texts, and extract data using a standardized data extraction form. Disagreements will be resolved through discussion or consultation with a third reviewer. Extracted data will include study characteristics, population characteristics, MRI timing, fetal brain abnormality type, MRI findings or biomarkers, postnatal follow-up duration, outcome assessment tools, and effect estimates or raw data required for meta-analysis. The study selection process will be documented using a PRISMA flow diagram.

Quality assessment / Risk of bias analysis Risk of bias will be assessed according to study type. Prognostic factor studies will be assessed using the Quality in Prognosis Studies (QUIPS) tool. Diagnostic or prognostic accuracy studies will be assessed using QUADAS-2-informed domains, including patient selection, index test, reference standard, and flow/timing. Prediction model, artificial intelligence, and radiomics studies will be assessed using PROBAST-informed and QUADAS-AI-informed considerations, including participant selection, predictor definition, outcome assessment, model overfitting, validation, calibration, and clinical applicability.

Small descriptive series and case-based narrative evidence will not be assigned pooled risk-of-bias ratings but will be summarized descriptively, with limitations clearly stated.

Strategy of data synthesis We will conduct a structured narrative synthesis and evidence map across all prenatal MRI biomarker domains. Each MRI biomarker domain will be classified according to clinical translation readiness: meta-analysis possible, prognostic accuracy/core evidence, small cohort 2×2 evidence, limited/reported/secondary evidence, diagnostic/biometric evidence only, or insufficient/narrative evidence.

Random-effects meta-analysis will be performed only when at least two clinically comparable studies report extractable numerators and denominators or compatible effect estimates. Ventriculomegaly-specific analyses will be prioritized because this domain has the most extractable and comparable outcome data. Planned ventriculomegaly analyses include overall adverse neurodevelopmental or neurologic outcome rate, severity categories, laterality, progression, and isolated versus non-isolated status when data permit.

For proportion meta-analysis, pooled adverse outcome rates will be estimated using random-effects models. For comparative analyses, odds ratios or risk ratios will be synthesized when events and denominators are available. Heterogeneity will be assessed using I^2 and interpreted clinically rather than only statistically. When quantitative pooling is inappropriate, findings will be summarized in the evidence map and narrative synthesis.

Subgroup analysis Planned subgroup and sensitivity analyses will include fetal condition category, ventriculomegaly severity, unilateral versus bilateral ventriculomegaly, progressive versus stable or regressive ventriculomegaly, isolated versus non-isolated abnormality, standardized versus non-standardized neurodevelopmental assessment, follow-up age of at least 24 months, genetic or infection testing status, and cohort-overlap risk.

Congenital aqueductal stenosis or severe hydrocephalus will be analyzed separately from mild-to-moderate ventriculomegaly because of differences in etiology, severity, intervention, and expected neurologic outcomes.

Sensitivity analysis Sensitivity analyses will be performed to examine the robustness of the

findings. Planned sensitivity analyses include excluding studies at high risk of bias, studies with follow-up duration shorter than 12 months, studies without standardized neurodevelopmental assessment, studies with incomplete reporting of MRI findings or outcomes, and studies with very small sample sizes. Additional sensitivity analyses may be conducted according to study design, outcome definition, or availability of adjusted effect estimates.

Language restriction No language restriction will be applied during the database search. Non-English studies will be translated when feasible.

Country(ies) involved China.

Other relevant information Amendment: After full-text verification and preliminary data extraction, the synthesis strategy was refined from a broad systematic review and meta-analysis to a systematic review, evidence map, and ventriculomegaly-focused meta-analysis. This change was made because extractable biomarker-outcome data were sparse and heterogeneous outside ventriculomegaly. The review question, population, exposure/index factors, and primary outcome remain unchanged. The amendment clarifies that quantitative synthesis will be restricted to clinically comparable biomarker-outcome pairs with extractable event data or compatible effect estimates, while other MRI biomarker domains will be summarized using an evidence map and narrative synthesis.
The amendment also clarifies risk-of-bias assessment by study type: QUIPS for prognostic factor studies, QUADAS-2-informed assessment for diagnostic or prognostic accuracy studies, and PROBAST/QUADAS-AI-informed considerations for prediction model, AI, and radiomics studies.

Keywords fetal MRI; prenatal MRI; fetal brain abnormalities; neurodevelopmental outcome; prognostic biomarker; meta-analysis.

Dissemination plans The findings of this systematic review and meta-analysis will be submitted for publication in a peer-reviewed neurology, fetal medicine, or medical imaging journal. The results may also be presented at relevant academic conferences. The review aims to inform prenatal counseling, postnatal risk stratification, and future research on fetal brain MRI biomarkers.

Contributions of each author

Author 1 - Gan Tian - Author 1 conceived the review, developed the protocol, designed the search strategy and eligibility criteria, and will supervise study selection, data extraction, risk of bias assessment, data synthesis, and manuscript drafting.
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