



# The Incremental Yield of CMA over Karyotype in Isolated Absent/Hypoplastic Nasal Bone—A Systematic Review and Meta-Analysis

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## 1. BACKGROUND / OBJECTIVE

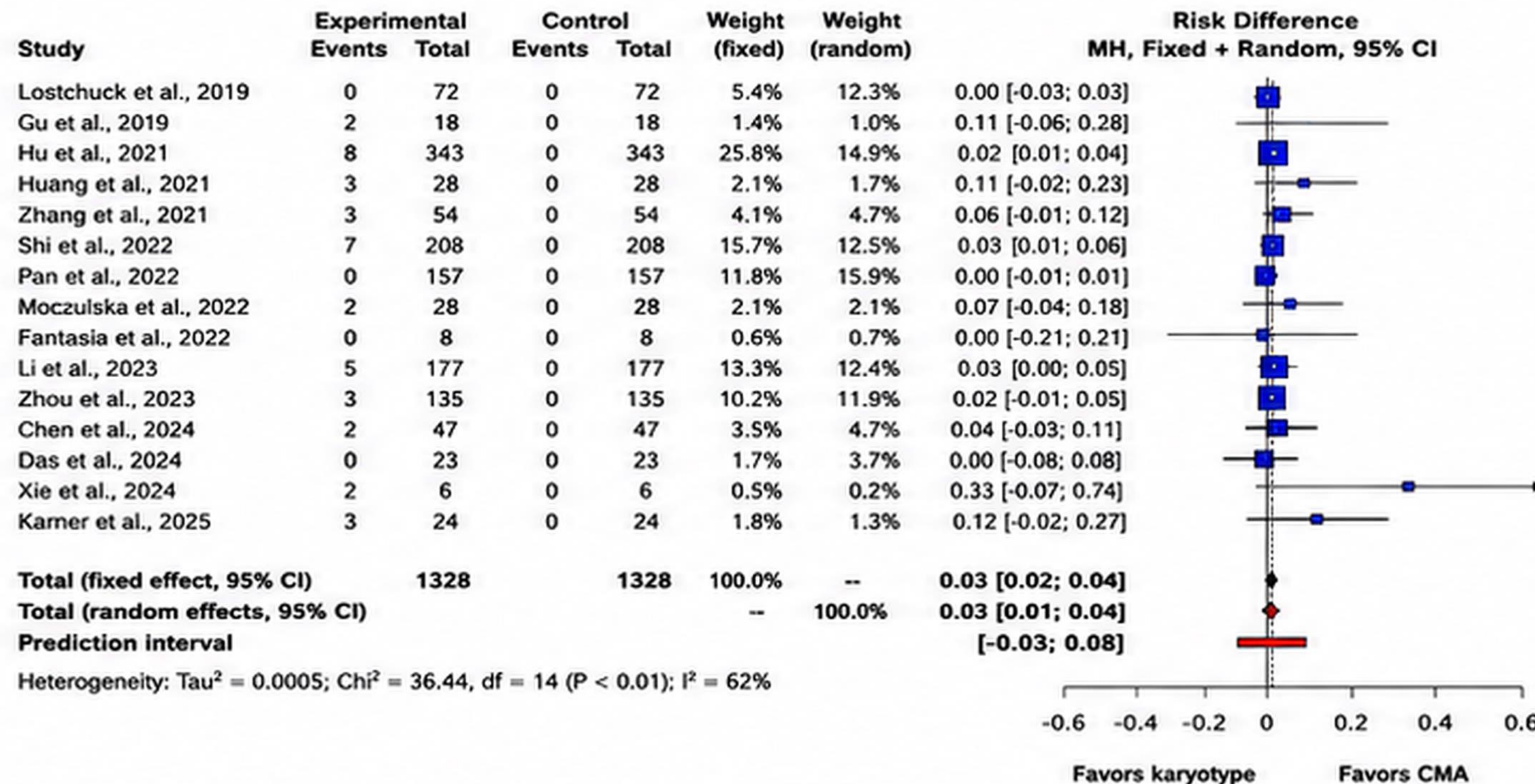
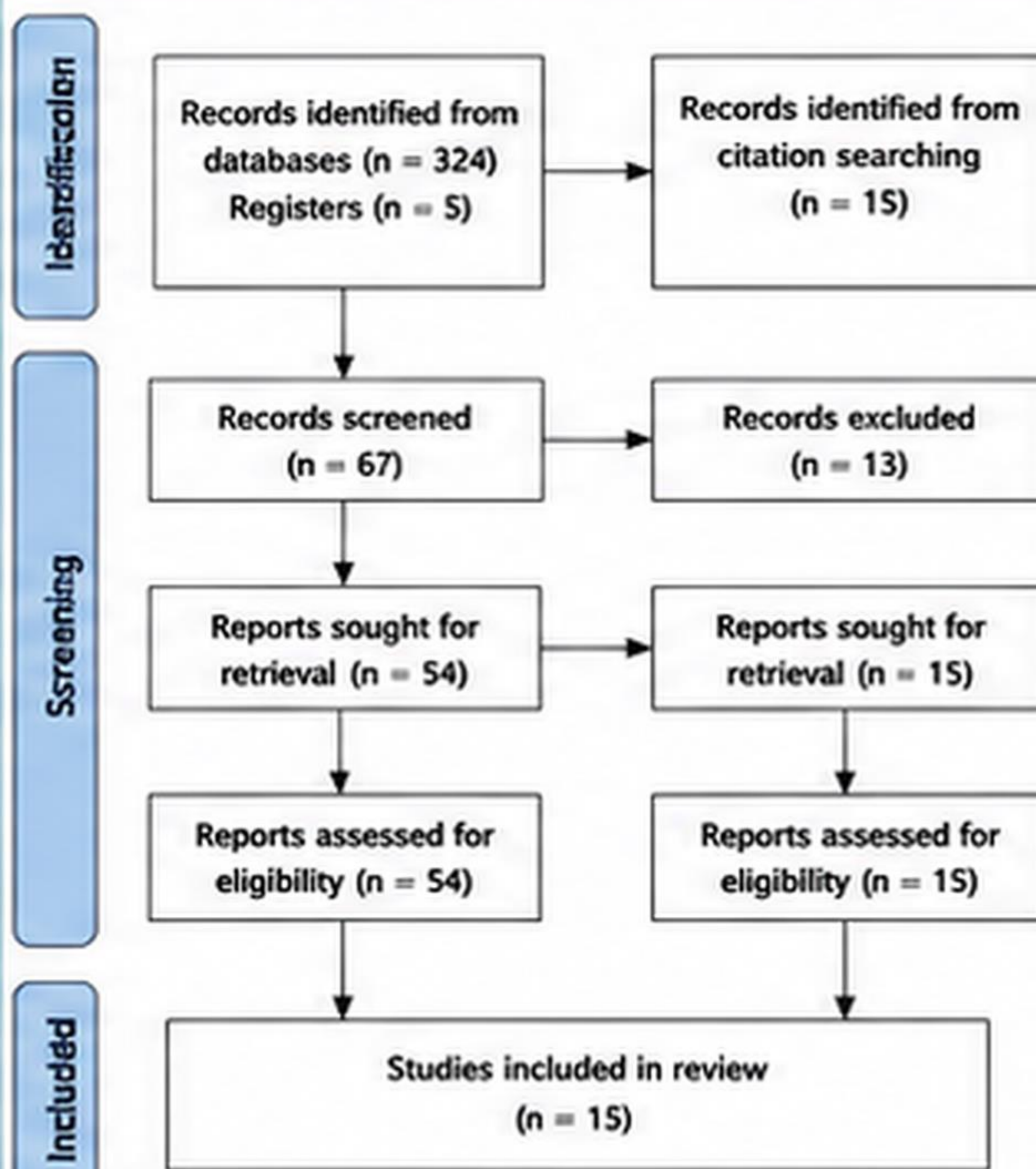
- Absent or hypoplastic fetal nasal bone is strongly associated with Trisomy 21 and other common aneuploidies.
- Karyotyping detects major chromosomal abnormalities but cannot identify submicroscopic copy number variants (CNVs).
- Objective:** To evaluate the incremental diagnostic yield of chromosomal microarray analysis (CMA) over standard karyotyping in fetuses with isolated absent or hypoplastic nasal bone, without additional structural abnormalities or soft markers.



## 2. METHODS

- Systematic review and meta-analysis conducted according to PRISMA and MOOSE guidelines.
- PROSPERO registration: CRD420251241819.
- Databases searched: Medline, Scopus, ClinicalTrials.gov, EMBASE, CENTRAL, and Google Scholar.
- Last search date: 30 November 2025.
- Included study types: observational studies reporting CMA findings in isolated absent/hypoplastic nasal bone.
- Total studies included: 15.
- Total fetuses included: 1328.
- Variants of uncertain significance were excluded.
- Risk differences were pooled using inverse variance weighting; heterogeneity assessed with  $I^2$ .

## 3. STUDY SELECTION



## KEY RESULTS



**15 studies**



**1328 fetuses**



**Pooled incremental yield of CMA over karyotype: 3%**



**95% CI: 1%–4%**



**Heterogeneity:  $I^2 = 62\%$**



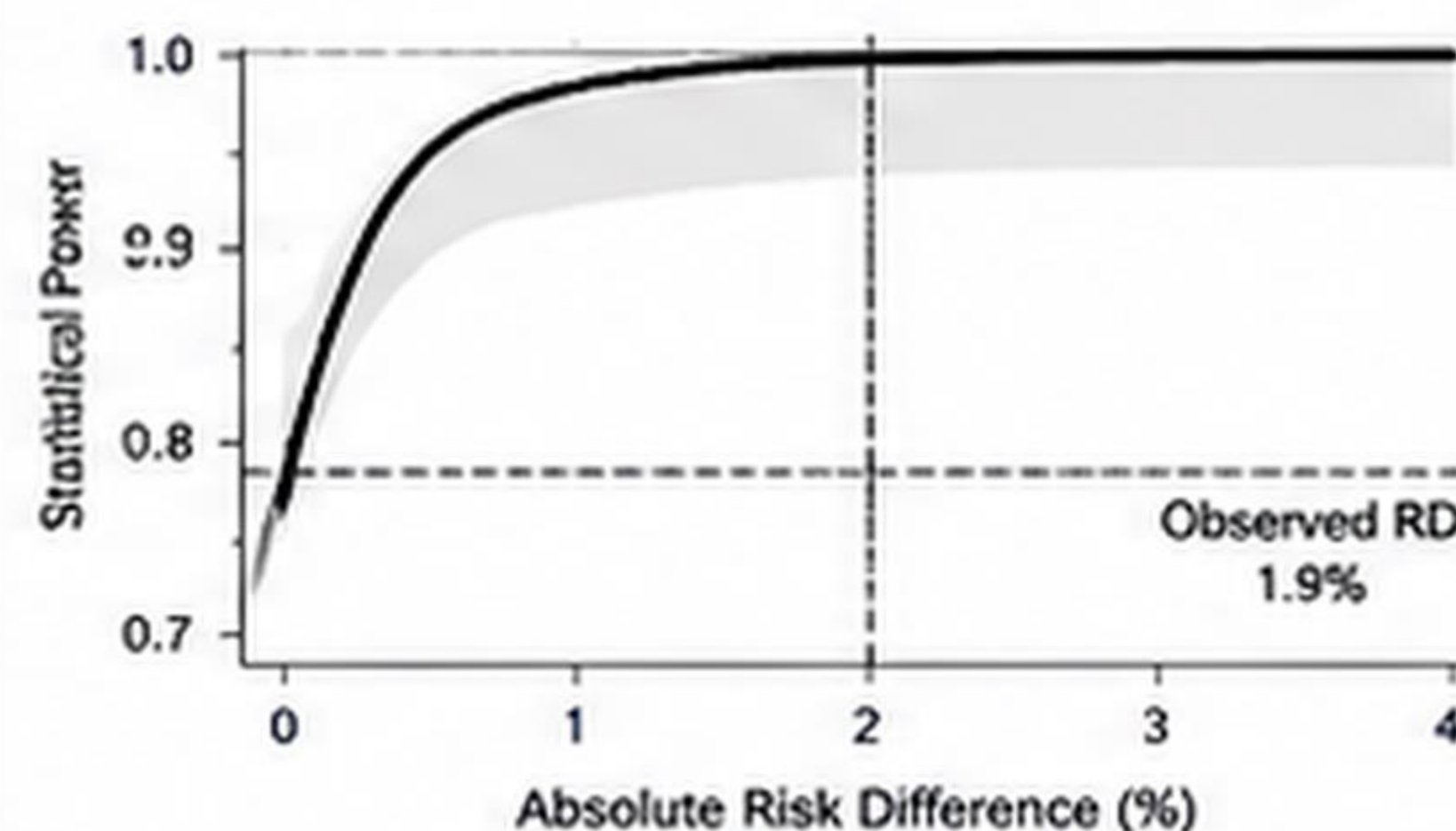
**Observed study-specific incremental yield range: 0%–33%**

### Interpretation

- The pooled data showed an overall 3% incremental yield of CMA over karyotyping in isolated absent/hypoplastic nasal bone.
- This indicates that a small but clinically meaningful proportion of pathogenic submicroscopic CNVs would be missed by conventional karyotyping alone.

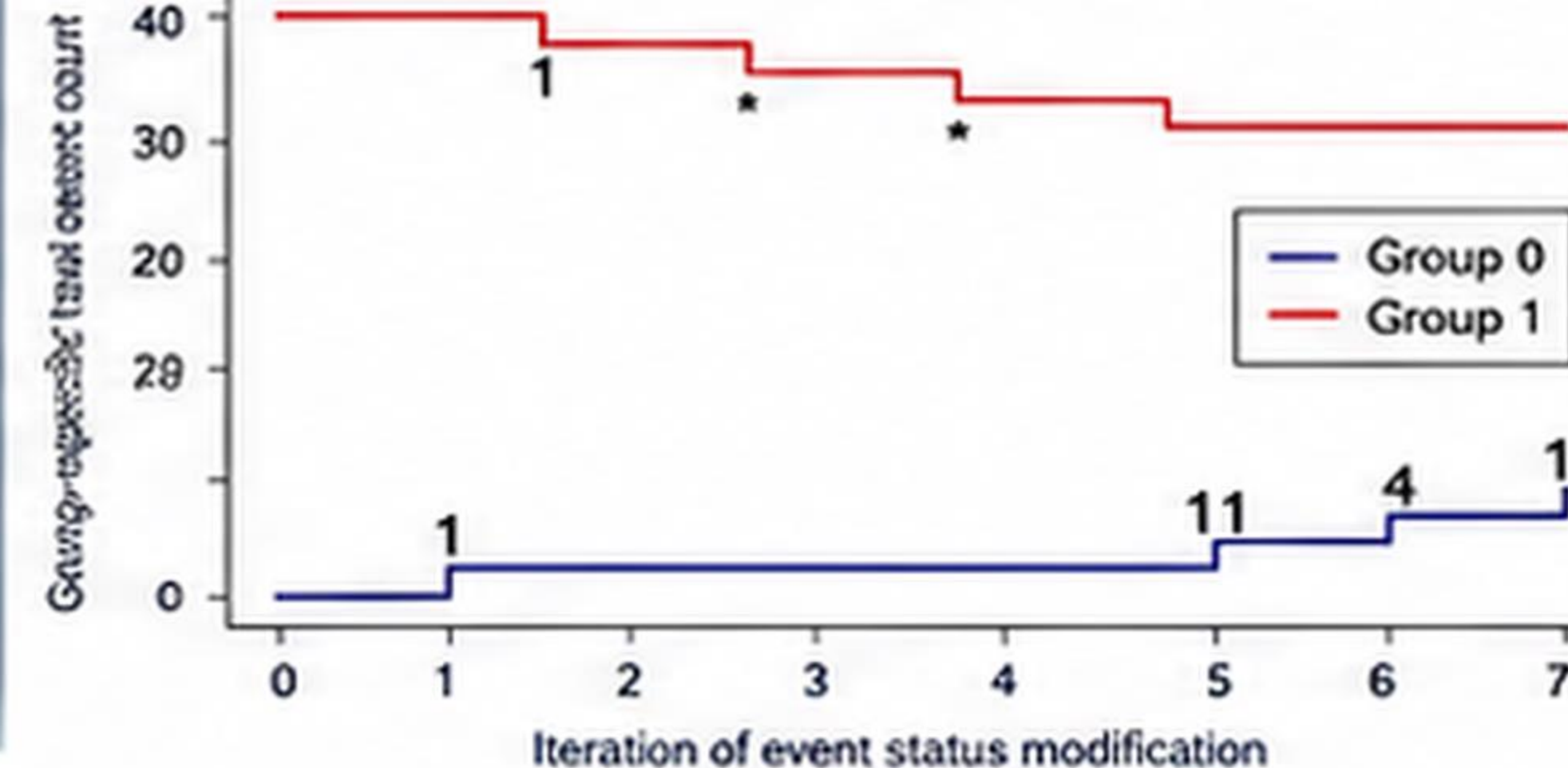
## 5. ROBUSTNESS OF FINDINGS

### A) STATISTICAL POWER



- Post hoc power to detect the observed absolute risk difference of 1.9% was >99.9%.
- Approximate power remained ~96% for a 1.0% absolute increase.
- An absolute risk difference of about 0.6% corresponded to ~80% power.

### B) FRAGILITY ANALYSIS



- Fragility index (FI): 7.
- Fragility quotient (FQ): 0.3%.
- Statistical significance was lost after seven event changes.

*Fragility reflects the rarity of pathogenic CMA findings rather than instability of the analysis.*

## 6. STRENGTHS & LIMITATIONS



### Strengths

- First meta-analysis focused specifically on isolated absent/hypoplastic nasal bone.
- Included all available studies up to date.
- Excluded variants of uncertain significance.



### Limitations

- Heterogeneity in the definition of hypoplastic nasal bone across studies.
- Several studies spanned long recruitment periods, potentially reflecting different ultrasound technologies.
- Residual heterogeneity remained moderate.



## 7. CONCLUSION / CLINICAL IMPLICATIONS

**CMA provides an overall 3% incremental diagnostic yield over karyotyping in fetuses with isolated absent or hypoplastic nasal bone. These findings support consideration of CMA in counseling and individualized prenatal management when this common soft marker is detected.**

