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Dynamics of Embryo Sex Ratio in IVF/ICSI: A Systematic Review and Meta-Analysis of Genetically Confirmed Embryos

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Systematic Review

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Abstract

Purpose

To investigate deviation from sex-ratio balance in IVF/ICSI embryo cohorts with genetically confirmed sex, and whether pre-fertilisation sperm enrichment or post-fertilisation embryo-selection markers are associated with embryo sex.

Methods

Systematic review and meta-analysis registered in PROSPERO (CRD420261354601). MEDLINE, Embase, CENTRAL, Scopus, and additional sources were searched for eligible human IVF/ICSI studies with embryo-level genetic sex confirmation and extractable male and female embryo counts. Single-arm male proportions were pooled using logit-transformed random-effects meta-analysis with Hartung–Knapp–Sidik–Jonkman (HKSJ) correction; comparative analyses used Mantel–Haenszel odds ratios. Risk of bias was assessed using NOS, ROBINS-I, or QUADAS-2, as applicable.

Results

Thirty study records (38 analytic arms) were included. The primary post-fertilisation proportion meta-analysis comprised 23 arms (28,244 embryos). Pooled male embryo proportion: 0.487 (95% CI 0.463–0.512), crossing 0.50, indicating no significant deviation from sex-ratio balance (I^2 = 89.1%; τ^2 = 0.0441; prediction interval 0.378–0.598). Era subgroup analysis showed a significant between-group difference (χ^2 = 9.20, df = 2, p = 0.010). Family-balancing cohorts: pooled proportion 0.512 (95% CI 0.445–0.579; I^2 = 0.0%), crossing 0.50. Eight pre-fertilisation arms (four papers) were analysed separately: male-selection arms pooled at 0.70 (95% CI 0.42–0.88) and female-selection at 0.21 (95% CI 0.11–0.37); between-subgroup difference p < 0.0001. The secondary comparative meta-analysis (12 comparisons) yielded OR 1.05 (95% CI 0.85–1.29); no post-fertilisation marker showed a significant association with embryo sex.

Conclusions

Embryo sex distribution after routine IVF/ICSI is broadly balanced. Non-invasive post-fertilisation markers are not dependable sex-prediction tools; sperm sorting shifts probabilities only in technique-specific settings. PROSPERO: CRD420261354601.

Capsule Summary

Pooled analysis of 28,244 genetically confirmed post-fertilisation IVF/ICSI embryos across 23 analytic arms demonstrates that embryo sex distribution is broadly balanced (male proportion 0.487; 95% CI 0.463–0.512). Non-invasive post-fertilisation markers cannot reliably predict embryo sex; only intentional pre-fertilisation sperm sorting produces a clinically meaningful directional shift in sex distribution.

Introduction

The determinants of the human sex ratio have long been a subject of biological and clinical interest. At the population level, the sex ratio at live birth is remarkably stable, with a slight male predominance of approximately 105–106 males per 100 females, a pattern largely attributed to sex-differential survival across gestation [1, 2]. At the embryo level, Orzack et al. [2] karyotyped nearly 140,000 embryos from ART cycles and demonstrated that the sex ratio at conception was not significantly different from the 50:50 Mendelian expectation, constituting the reference against which the effect of any ART intervention on sex distribution must be formally evaluated [2, 3].

There has been substantial global interest in family balancing the selection of embryo sex for non-medical reasons [4]. Sex selection for medical indications such as X-linked genetic disorders is widely accepted as an integral component of PGT-M [4, 5]. Non-medical sex selection remains ethically debated and variably regulated: prohibited in the United Kingdom, Australia, Canada, France, Germany, and India, while legally permissible in the United States and several other countries [5, 6]. Fertility specialists are therefore frequently under direct pressure from patients to endorse methods capable of predicting or enriching for a desired embryo sex [6, 7].

Two broad categories of intervention are commonly discussed. Pre-fertilisation approaches aim to alter the proportions of X-bearing and Y-bearing spermatozoa that reach the egg before fertilisation. Post-fertilisation approaches examine whether observable embryo characteristics, morphology, developmental timing, morphokinetics, and AI-based assessment are associated with embryo sex [8–10]. These two categories operate through fundamentally distinct biological mechanisms and carry different levels of evidence.

The most conceptually direct pre-fertilisation approach is flow cytometry-based sperm sorting (MicroSort®), which exploits the approximately 2.8% difference in DNA content between X-bearing and Y-bearing spermatozoa. Over a thirteen-year clinical programme, Karabinus et al. [9] reported mean post-sort purities of 87.9% for X-chromosome-enriched and 73.4% for Y-chromosome-enriched fractions. Density gradient centrifugation and the albumin gradient separation (Ericsson) method represent older approaches; multiple controlled FISH studies have failed to demonstrate reliable sex-chromosome enrichment beyond chance [11].

At the post-fertilisation level, blastulation day has attracted the most attention, with several retrospective studies reporting a higher proportion of male embryos among Day-5 blastocysts than among Day-6 or later blastocysts [12, 13]. TE and ICM morphological grade have similarly been proposed as sex-associated features [12, 14]. Morphokinetic parameters have been investigated with conflicting results [15–17]; no morphokinetic model has achieved discriminatory accuracy approaching clinical utility in independently validated cohorts [18].

PGT-A currently represents the only diagnostically definitive method for confirming embryo sex before transfer [19, 20]. Studies relying solely on live birth sex do not provide valid data on embryo sex distribution, as birth sex represents a combination of embryo sex, implantation probability, ongoing pregnancy rates, and transfer selection decisions that cannot be separated without embryo-level confirmation [21].

Despite the volume of published research in this area, the evidence base remains fragmented and methodologically diverse. Specific problems include inconsistently defined outcome levels [2, 21]; a combination of legacy Day-3 FISH analyses with contemporary PGT-A/NGS cohorts [22, 23]; evaluation of pre-fertilisation interventions alongside post-fertilisation markers; diverse study populations [24]; and often inappropriate statistical methods for proportion-level data [25].

The clinical imperative to address these gaps is shaped by five intersecting developments. First, delayed family starting limits the number of embryos available per cycle; pursuing unproven sex-selection strategies carries real biological and financial costs [6]. Second, increasing inter-child spacing intensifies family-balancing demand as biological fertility declines further [7]. Third, the persistent myth that routine ART procedures can preferentially generate embryos of a desired sex leads couples to undergo expensive and often futile interventions [4, 6]. Fourth, in jurisdictions where non-medical sex selection is prohibited, patients frequently pursue costly cross-border reproductive care [26]. Fifth, the financial cost of medical tourism for family balancing is substantial, with IVF cycles including PGT-A in popular destinations ranging from USD 8,000 to 25,000 per cycle [7].

The present systematic review and meta-analysis were undertaken to synthesise all available embryo-level evidence to answer the questions couples are actually asking: whether standard ART procedures alter embryo sex distribution, whether non-invasive markers can predict embryo sex, and whether any pre-fertilisation technique can reliably enrich for a desired sex.

Aims and Objectives

The primary objective is to determine the pooled proportion of male embryos among all chromosomally confirmed embryos in IVF/ICSI cohorts and to assess whether this proportion deviates significantly from the expected baseline of 0.50.

Secondary objectives are: (i) to quantify the effect of pre-fertilisation sperm-enrichment techniques on embryo sex distribution; (ii) to evaluate whether non-invasive post-fertilisation embryo characteristics are independently associated with a statistically significant alteration in male embryo proportion; (iii) to examine the influence of population type, general IVF/PGT cohorts versus family-balancing cohorts, on observed sex ratios.

Methods

This systematic review and meta-analysis were conducted in accordance with the PRISMA 2020 statement (Fig. 1 and Table 1) [27]. This study was registered on PROSPERO (CRD420261354601).

Eligibility Criteria

Eligibility criteria are summarised in Table 1 (PICO eligibility criteria). Eligible studies included couples undergoing IVF/ICSI whose embryos' sex was genetically confirmed at the embryo level using PGT-A, PGS, PGD/FISH, aCGH, PCR on embryo cells or blastomeres, or a similar chromosomal approach with at least five embryos. Extractable counts of male and female embryos were crucial. Eligible studies included pre-fertilisation sperm-enrichment methods and post-fertilisation non-invasive embryo characteristics (Fertilization methods (IVF/ICSI), TE grade, ICM grade, blastulation day, cleavage speed, morphokinetics, AI/ML scoring, and metabolomics). Animal studies, reviews, editorials,

conference abstracts without extractable data, studies reporting only live-birth sex, and non-English language publications without available translation were excluded.

Table 1
PICO eligibility criteria.

Domain	Included	Excluded	Notes
Population	Human IVF/ICSI embryo cohorts; embryo-level sex confirmation by PGT-A, PGS, PGD/FISH, aCGH, or PCR; extractable male/female counts; ≥5 embryos	Animal studies; live-birth-only sex outcomes without embryo-level confirmation; PGT-M studies where sex is incidental; reviews/editorials/letters; <5 embryos	Birth sex introduces transfer selection bias and differential implantation unrelated to embryo-level evaluation
Intervention / Exposure	• Pre-fertilisation: flow cytometry sorting (MicroSort® or equivalent), density gradient with sex-enrichment intent, albumin gradient (Ericsson method), novel sperm preparation with sex enrichment as stated outcome. • Post-fertilisation: TE grade, ICM grade, blastulation day, cleavage speed Day 2–3, morphokinetics (t2–tB, cc2, s2), AI/ML applied to embryo images or time-lapse data, metabolomics of spent culture medium	Studies where accuracy confirmation relied exclusively on FISH or flow cytometry on sorted sperm without downstream embryo-level chromosomal confirmation. Exception: sperm-sorting studies tested by downstream PGT-A are eligible	Studies reporting any single method or combination of eligible methods were included
Comparator	• Single-arm studies: no formal comparator; reference = male proportion 0.50. • Comparative studies: alternative exposure category within the same study (e.g. TE-A vs TE-B/C, Day 5 vs Day 6/7, sperm sorting vs standard preparation)	Birth sex as reference standard; external registry cohorts used as shared control across independent observational studies	Birth sex is explicitly excluded throughout
Outcomes (Primary)	Pooled proportion of male embryos among genetically confirmed embryos. Deviation = 95% CI excluding 0.50	Live birth sex ratio as primary outcome	Reference value: male proportion 0.50
Outcomes (Secondary)	OR/RR for comparative studies; associations between TE grade, ICM grade, blastulation day, morphokinetics, AI scoring and embryo sex	—	See Online Resource 1, Supplementary Table S2
Study Designs	RCTs, prospective cohort, retrospective cohort, case-control, cross-sectional embryo-cohort, secondary analyses. Conference abstracts if sufficient extractable data	Reviews, editorials, letters, commentaries. Conference abstracts without sufficient data. Non-English publications without translation	—

PICO, Population/Intervention/Comparator/Outcome; PGT-A, preimplantation genetic testing for aneuploidy; TE, trophectoderm; ICM, inner cell mass; AI/ML, artificial intelligence/machine learning.

Literature Search

A systematic search was performed on MEDLINE (via PubMed), Embase (via Ovid), CENTRAL, the Cochrane Library, Google Scholar and Scopus; ClinicalTrials.gov and SCI were also searched. No date restriction was applied. Reference lists were hand-searched. Three conceptual domains were combined with Boolean AND: (i) sperm-sorting and sex-selection methods; (ii) embryo or offspring sex distribution; (iii) assisted reproduction context. The complete search strings are in Supplementary File 1.

Study Selection and Data Extraction

Study Selection and Data Extraction

Records were deduplicated and subsequently imported into Rayyan (rayyan.ai). Two reviewers independently conducted title and abstract screening; a random sample of 20% was separately re-evaluated by a third reviewer (Cohen's kappa threshold > 0.70). Eligibility for full-text inclusion was evaluated by two reviewers, with ambiguities addressed by a third. Data extraction employed a consistent pre-defined form, with 20% of records independently validated by a third reviewer. The extracted fields comprised: first author; year; country; study design; IVF/ICSI procedure; intervention/exposure; sample size; sex confirmation method; counts of male and female embryos; subgroup counts when reported; ploidy status; confounders; and risk-of-bias score.

Risk of Bias Assessment

Risk of bias was assessed independently by two reviewers, with discrepancies resolved by a third. The NOS was applied to retrospective and prospective cohort studies. ROBINS-I was applied to non-randomised comparative studies across seven domains. QUADAS-2 was applied to diagnostic or predictive accuracy studies (AI-based morphokinetic models; metabolomic classifiers). All studies were additionally assessed for enriched or family-balancing cohort recruitment bias. GRADE was not formally applied; a narrative certainty summary is provided in the Discussion.

Statistical Analysis

Primary meta-analysis. Single-arm proportion meta-analysis of pooled male embryo proportion using logit transformation (sm = 'PLOGIT') with random-effects framework and HKSJ correction (metaprop, meta package, R v4.5.3). Pre-specified sensitivity analysis: Freeman–Tukey double arcsine transformation (sm = 'PFT'). Reference value: male proportion = 0.50; deviation defined as 95% CI excluding 0.50.

Secondary meta-analysis. Pooled odds ratios (OR) via Mantel–Haenszel method, random-effects with HKSJ correction (metabin). Male embryo = event; female = non-event in all 2×2 tables. Blastulation-day analysis restricted to studies with separate denominators; Day 5 = experimental arm; Day 6/7 = comparator.

Heterogeneity and subgroup analyses. I^2 and Cochran's Q. Four pre-specified subgroup analyses: (i) selection-bias group; (ii) genetic era; (iii) intervention category; (iv) blastulation day. Pre-specified sensitivity analyses: leave-one-out; low risk-of-bias restriction; PGT-A/NGS-only restriction; ≥100 embryos restriction; exclusion of Karabinus 2014 [9]. Publication bias: contour-enhanced funnel plot with Egger's test where $k \geq 10$. Exploratory meta-regression using REML (rma, metafor package) where $k \geq 10$.

Results

Study Selection

The systematic database and supplementary searches identified 148 records after deduplication. Six databases were searched: MEDLINE (via PubMed), Embase (via Ovid), CENTRAL (Cochrane Central Register of Controlled Trials), Scopus, ClinicalTrials.gov, and SCI. These were supplemented by Google Scholar, reference list hand-searching, and forward citation searching for key studies, which did not yield additional unique records. After title and abstract screening by two independent reviewers, with 20% random independent re-screening by a third reviewer (Cohen's kappa threshold > 0.70), 99 records were excluded, and 49 full-text reports were sought for retrieval. All 49 full-text reports were successfully obtained. After an independent full-text eligibility assessment by two reviewers, with uncertainties resolved by a third, 19 reports were excluded with categorised reasons.

The 19 excluded full-text reports fell into seven categories: six reported live birth or transfer-level outcomes only [21, 55, 56, 57, 58, 68]; two had a structurally truncated or sex-balanced denominator by design [53, 54]; four lacked extractable embryo-level sex data or reported wrong outcomes [59, 61, 62, 17]; two confirmed sex by birth outcome only without embryo-level chromosomal verification [60, 71]; two were mechanistic, wrong-design, or review-type publications without usable data [52, 63]; one was a conference abstract without a sufficient peer-reviewed publication [72]; and two were excluded for other reasons (non-English without translation; transcriptomic review without extractable data) [65, 66].

Thirty study records were retained, contributing 38 analytic arms. Twenty-three post-fertilisation arms (28,244 embryos) entered the primary proportion meta-analysis. Eight pre-fertilisation arms from four source papers (8,963 embryos: Karabinus 2014 XSort n = 3,563; Karabinus 2014 YSort n = 3,921; Cheung 2023 male-selection n = 280; Cheung 2023 female-selection n = 292; Elias 2022 male-enrichment n = 292; Elias 2022 female-enrichment n = 301; Setti 2012 ICSI n = 104; Setti 2012 IMSI n = 210) were analysed separately and excluded from the primary meta-analysis denominator. Seven study records contributed 12 within-study comparative contrasts to the secondary odds-ratio meta-analysis. Two studies provided data for narrative synthesis only. The PRISMA 2020 flow diagram is presented in Fig. 1.

Study Characteristics

Included studies were published between 2001 and 2026 and originated from 14 countries. The evidence base comprised contemporary blastocyst-stage PGT-A/NGS cohorts, legacy non-Day-3 chromosomal platforms, Day-3 PGD/FISH studies, family-balancing cohorts, and pre-fertilisation sperm-enrichment studies. Sample sizes ranged from small pilot cohorts to large registry-style PGT-A datasets. Study characteristics are summarised in Table 2; studies excluded at full-text review with reasons are presented in Table 3.

Table 2. **Characteristics of included studies**

Table 2
Study characteristics of the included studies30 studies included: post-fertilisation (23) + pre-fertilisation (3) + secondary MA only (2) + narrative AI (2).

No.	First Author	Country	Design	Genetic Method	Stage	Male n	Female n	Total n	Analysis	Notes / Citation
Section A — Post-fertilisation: Contemporary PGT-A / NGS / PGS blastocyst cohorts (n = 11)										
1	Carrasco 2022 [12]	Spain	Retro cohort	PGT-A (NGS)	Blast	540	546	1,086	1° MA	Euploid blastocysts; sex-ratio cohort
2	Moutos 2021 [28]	USA	Retro cohort	PGT-A	Blast	898	911	1,809	1° + 2° MA	TE, ICM, blastulation-day comparators
3	Kulmann 2021 [29]	Brazil	Retro cohort	PGT-A (NGS)	Blast	303	317	620	1° + 2° MA	TE, ICM, blastulation-day comparators
4	Nogueira 2024 [30]	UAE	Retro cohort	PGT-A (NGS)	Blast	1,445	1,535	2,980	1° MA	Combined euploid CS + NCS
5	Wang 2018 [31]	USA	Retro cohort	PGS	Blast	321	307	628	1° MA	24-chromosome PGS; morphology
6	Georgiou 2025 [32]	Australia	Retro cohort	PGT-A	Blast	1,323	1,285	2,608	1° MA	Euploid blastocyst cohort
7	So 2026 [33]	USA	Retro cohort	PGT-A	Blast	625	573	1,198	1° MA	Conference poster
8	Roberts 2018 [13]	USA	Retro cohort	PGT-A (NGS)	Blast	258	207	465	1° MA	All sex-confirmed blastocysts; maternal age 35.2 yrs
9	Popa 2024 [34]	UK	Retro cohort	PGT-A	Blast	844	794	1,638	1° MA	AI morphokinetics; embryo sex prediction; euploid embryos
10	Liu 2019 [35]	USA	Retro cohort	PGT-A	Blast	350	320	670	1° + 2° MA	Day 5 vs Day 6 blastulation comparator; 21 embryos unclassified
11	Woo 2020 [74]	USA	Retro cohort	PGT-A	Blast	670	685	1,355	1° MA	Control arm only; counts derived from reported percentages.
Section B — Post-fertilisation: Legacy non-day-3 cohorts (aCGH/PGS blastocyst) (n = 5)										
12	Alfarawati 2011 [36]	USA	Retro cohort	PGS	Blast	112	105	217	1° MA	Legacy PGT cohort; morphology study
13	Zhang Robins 2017 [41]	USA	Retro cohort	PGS	Blast	156	215	371	1° MA	Counts reconstructed from Day 5/6 percentages
14	Grunert 2015 [39]	USA	Retro cohort	aCGH	Blast	649	608	1,257	1° MA	TE-biopsy euploid aCGH cohort

Section A — Post-fertilisation: Contemporary PGT-A / NGS / PGS blastocyst cohorts (n = 11)										
No.	**First Author**	**Country**	**Design**	**Genetic Method**	**Stage**	**Male n**	**Female n**	**Total n**	**Analysis**	**Notes / Citation**
15	Eaton 2011 [40]	USA	Retro cohort	PGS	Blast	392	366	758	1° MA	First PGS cycles 2006–07; XX/XY counts explicit
16	Orteiro 2021 [75]	Brazil	Prospective	PGT-A	Blast	8	12	20	1° MA	Metabolomics sex prediction; euploid embryos; small n
Section C — Post-fertilisation: Day-3 PGD / FISH era (n = 7)										
17	Kirshenbaum 2019 [44]	Israel	Retro cohort	PGD/FISH	Day-3	41	36	77	1° MA †	Family-balancing cohort; diagnosed embryos
18	Zeyad 2018 [37]	Saudi Arabia	Retro cohort	PGD/FISH	Day-3	227	189	416	1° + 2° MA	Morphokinetics; Day-5 blastulation comparator
19	Abotalib 2013 [38]	Saudi Arabia	Retro cohort	PGD/FISH	Day-3	212	300	512	1° MA	Day-3 PGD sex-ratio cohort
20	Malpani 2002 [43]	India	Retro cohort	PGD/FISH	Day-3	131	111	242	1° MA †	Family balancing; euploid only (aneuploids excluded)
21	Sindiani 2021 [24]	Jordan	Retro cohort	PGD/FISH	Day-3	289	296	585	1° MA †	Family-balancing cohort
22	Iaconelli 2010 [42]	Brazil	Prosp RCT	FISH	Day-3	156 ‡	237 ‡	393 ‡	1° + 2° MA	ICSI vs IMSI; combined arm in primary MA; separate arms in secondary MA
23	Setti 2012 [15]	Brazil	Prosp RCT	PGD/FISH	Day-3	116 ^	198 ^	314 ^	1° MA (2 arms)	ICSI arm (46M/58F); IMSI arm (70M/140F); euploid counts
Section D — Pre-fertilisation: Sperm-level sex-enrichment methods (n = 3 papers, 7 analysis arms)										
24	Cheung 2023 [14]	USA	Non-RCT	PGT-A	Blast	3,054□ /223□ /61□	3,718□ /57□ /231□	6,772□ /280□ /292□	1° MA (3 arms)	SST (sperm sex-selection technique); □ctrl euploid; □M-select; □F-select
25	Karabinus 2014 [9]	USA	Prospective	FISH	Blast	2,515□ /510□	1,048□ /3,411□	3,563□ /3,921□	1° MA (2 arms) †	MicroSort flow cytometry; □Y-sort; □X-sort
26	Elias 2022 [45]	USA	Non-RCT	PGT-A	Blast	231□ /66□	61□ /235□	292□ /301□	1° MA (2 arms)	Novel dye-free multilayer density-gradient; □male-enrichment (231M/61F); □female-enrichment (66M/235F); PGT-A confirmed

Section A — Post-fertilisation: Contemporary PGT-A / NGS / PGS blastocyst cohorts (n = 11)										
No.	**First Author**	**Country**	**Design**	**Genetic Method**	**Stage**	**Male n**	**Female n**	**Total n**	**Analysis**	**Notes / Citation**
Section E — Secondary meta-analysis only (not in primary proportion MA) (n = 2)										
27	Munuera 2024 [76]	Spain	Retro cohort	PGT-A	Blast	681	633	1,314	2° MA only	Microfluidics vs density gradient
28	Palmerola 2019 [73]	USA	Retro cohort	PGT-A (NGS)	Blast	88□ / 231□	163□ / 493□	975	2° MA only	IVF vs ICSI fertilisation-method comparator. □IVF: 88M/163F (n = 251); □ICSI: 231M/493F (n = 724). OR = 3.07 (95% CI 1.49–6.28)
Section F — Narrative AI studies: qualitative synthesis only (n = 2)										
29	Zvereva & Dmitry 2022 [70]	Russia	Conf. abstract	Time-lapse AI	Blast	NR	NR	NR	Narrative AI	AI-based time-lapse scoring and male-female sex ratio
30	Liang 2026 [64]	USA/UK	Retrospective	Deep learning AI	Blast	NR	NR	NR	Narrative AI	Deep learning on time-lapse IVF movies; sex differences in pre-implantation development

Table 2 **footnotes and abbreviations**

† Family-balancing or biased-selection cohort; included in primary MA with selection_bias_group flag; sensitivity analysis excludes these studies.

‡ Iaconelli 2010: primary MA uses combined ICSI+IMSI pooled arm; secondary MA uses separate IMSI vs ICSI 2×2 table. Counts approximated from reported female percentages.

^ Setti 2012: primary MA uses two separate arms (ICSI: 46M/58F/104 total; IMSI: 70M/140F/210 total). Combined total shown for reference. Counted once in post-fertilisation (Section C).

NR = not reported. Blast = blastocyst stage. 1° MA = primary proportion meta-analysis (metaprop, logit, HKSJ). 2° MA = secondary comparative meta-analysis (metabin, OR, HKSJ). Pre-fert = pre-fertilisation (sperm-level) intervention. SecMA = secondary MA only. NarrAI = narrative AI synthesis only.

Pre-fertilisation source papers in Section D (n = 3): Cheung 2023, Karabinus 2014, and Elias 2022. Setti 2012 is counted once as post-fertilisation (Day-3 PGD/FISH era, Section C); its two arms are reclassified by enrichment target in the pre-fertilisation subgroup analysis.

Table 3
Excluded studies

No.	First Author	Country	Design	Excluded from	Reason for Exclusion / Citation
1	Bakkensen 2023 [21]	USA	Retro cohort	Both MAs	Live birth sex data only; no embryo-level sex counts extractable
2	Ray 1995 [52]	UK	Lab/mech. study	Both MAs	No intervention; mechanistic/laboratory study; no valid comparator
3	Huttler 2024 [53]	USA	Retro cohort	Both MAs	Data restricted to couples who expressed sex preference; structurally truncated denominator
4	Gill 2024 [54]	USA	Retro cohort	Both MAs	Inclusion criterion required ≥ 1 embryo of each sex: sex-balanced denominator by design; not a natural distribution
5	Arnold 2024 [55]	USA	Retro cohort	Both MAs	Transfer-level clinical outcomes only; no clean embryo-level male/female counts
6	Bayefsky 2023 [56]	USA	Retro cohort	Both MAs	Only families with existing children; total euploid embryos and per-sex counts not extractable
7	Zhao 2024 [57]	USA	Retro cohort	Both MAs	Only transferred embryo sex known; total euploid embryos not reported
8	Bain 2025 [58]	USA	Retro cohort	Both MAs	Euploid embryos selected for transfer only; not all generated/tested embryos included
9	Keshvar Y 2022 [71]	Iran	Retro cohort	Both MAs	Embryo sex not confirmed
10	Fugger 1998 [60]	USA	Non-RCT	Both MAs	Sperm sorting only; sex confirmation by birth, not embryo level
11	Liu 2020 [61]	Taiwan	Retro cohort	Both MAs	Chromosomal abnormalities and aneuploidies only; no embryo sex distribution data
12	Rojas-Pérez 2026 [62]	Mexico	Retro cohort	Both MAs	No PGT-A-confirmed embryo-level sex dataset extractable for meta-analysis
13	Klitzman 2013 [63]	USA	Survey/editorial	Both MAs	Wrong publication type/outcome; survey of clinicians' views on PGD, not an embryo-sex dataset
14	Kilbee 2023 [72]	UK	Conf. abstract	Both MAs	Conference abstract; full text unavailable or insufficient extractable data
15	Ferreux 2026 [65]	France	Review/summary	Both MAs	Wrong outcome; transcriptomic review/summary without extractable embryo sex-ratio data
16	Nasiri 2019 [66]	Iran	Retro cohort	Both MAs	No PGT-A/embryo-level chromosomal confirmation; non-invasive culture-medium biomarker only
17	Heiser 2023 [67]	Brazil	Retro cohort	Both MAs	PGT-A mosaicism profile study; no extractable male/female embryo sex-ratio dataset for this review
18	Shaia 2019 [68]	USA	Retro cohort	Both MAs	Registry/transfer-cycle sex-ratio data only; no embryo-level sex counts extractable
19	Fraire-Zamora 2023 [17]	Spain	Retro cohort	2° MA only	Embryo-level sex association reported, but 2×2 comparative data not extractable for the planned secondary meta-analysis

Risk of Bias

Most contemporary PGT-A/NGS cohort studies achieved higher NOS scores, particularly the larger cohort datasets from Moutos [28], Kulmann [29], Nogueira [30], Cheung [14], and Karabinus [9]. The main recurrent limitations were retrospective design, incomplete confounder adjustment, abstract-only data sources, and reconstructed counts derived from percentages. Family-balancing cohorts, including Sindiani [24] and the smaller clinical series, were additionally limited by enriched recruitment and patient preference bias. Non-randomised comparative analyses were generally rated at least moderate risk of bias because exposure allocation was not random and could be confounded by maternal age, ovarian reserve, embryo cohort size, laboratory practice, or transfer-selection rules. QUADAS-2 was applied only to AI, morphokinetic, or metabolomic studies; these were limited mainly by unclear external validation and uncertain clinical thresholds. The risk-of-bias assessment is summarised in Fig. 2.

Primary Analysis: Overall Proportional Meta-Analysis

The primary post-fertilisation proportion meta-analysis included 23 analytic arms from 21 source papers and 28,244 genetically confirmed embryos [9, 12, 13, 14, 15, 24, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44]. The pooled male embryo proportion was 0.487 (95% CI 0.463–0.512) using a random-effects logit-transformed model with HKSJ correction. The confidence interval crossed the expected reference value of 0.50, indicating no statistically significant deviation from sex-ratio balance. Heterogeneity was substantial (I^2 = 89.1%), and the prediction interval was wide (0.378–0.598), indicating that individual cohorts may vary whilst the overall pooled estimate remains close to balance (Fig. 3).

Figure 3 *Primary proportional meta-analysis of post-fertilisation cohorts (23 analytic arms; 28,244 genetically confirmed embryos). Random-effects logit-transformed model with Hartung–Knapp–Sidik–Jonkman (HKSJ) correction (metaprop, meta package, R v4.5.3). Pooled male embryo proportion: 0.487 (95% CI 0.463–0.512). The confidence interval crosses 0.50, indicating no statistically significant deviation from sex-ratio balance. Between-study heterogeneity: I^2 = 89.1%, τ^2 = 0.0441. Prediction interval: 0.378–0.598. The dashed vertical reference line is at 0.50 (expected sex-ratio balance).*

Subgroup Analyses: Primary Analysis

Pre-Fertilisation Categories

Eight pre-fertilisation arms from four source papers were analysed: Karabinus 2014 [9] (XSort male-target n = 3,563; YSort female-target n = 3,921); Cheung 2023 [14] (male-selection n = 280; female-selection n = 292); Elias 2022 [45] (male-enrichment n = 292; female-enrichment n = 301); and Setti 2012 [15] (ICSI n = 104, classified as male-selection; IMSI n = 210, classified as female-selection). Male-selection arms (4 arms; n = 4,239) yielded a pooled male embryo proportion of 0.70 (95% CI 0.42–0.88; I^2 = 94.2%; τ^2 = 0.5089). Female-selection arms (4 arms; n = 4,724) yielded a pooled male embryo proportion of 0.21 (95% CI 0.11–0.37; I^2 = 96.3%; τ^2 = 0.2359). The between-subgroup difference was highly significant (χ^2_1 = 23.51, df = 1, p < 0.0001) (Fig. 4), confirming directional enrichment in male-selection and depletion in female-selection groups. High within-group heterogeneity reflects variation across flow cytometry sorting, density gradient, and sperm injection protocols. Sensitivity analysis excluding Setti 2012 arms confirmed the directional finding was not dependent on the sperm injection comparison (Supplementary figure).

Figure 4 **Pre-fertilisation subgroup analysis by enrichment target (male-selection vs. female-selection arms). Eight arms from four source papers: Karabinus 2014** [9] **(XSort male-target n = 3,563; YSort female-target n = 3,921); Cheung 2023** [14] **(male-selection n = 280; female-selection n = 292); Elias 2022** [45] **(male-enrichment n = 292; female-enrichment n = 301); Setti 2012** [15] **(ICSI n = 104, male-selection comparator; IMSI n = 210, female-selection comparator). Random-effects logit-transformed model with Hartung–Knapp–Sidik–Jonkman (HKSJ) correction (metaprop, meta package, R v4.5.3). Male-selection arms (4 arms; n = 4,239): pooled male proportion 0.70 (95% CI 0.42–0.88; I^2 = 94.2%, τ^2 = 0.5089). Female-selection arms (4 arms; n = 4,724): pooled male proportion 0.21 (95% CI 0.11–0.37; I^2 = 96.3%, τ^2 = 0.2359). Between-subgroup difference: χ^2_1 = 23.51, df = 1, p < 0.0001. Overall (n = 8,963): 0.44 (95% CI 0.21–0.70); prediction interval 0.03–0.95. The dashed vertical reference line is at 0.50.**

Post-Fertilisation Cohorts

In post-fertilisation cohorts, where no intentional sperm-enrichment intervention was applied, the pooled estimate remained centred close to 0.50. This supports the interpretation that routine IVF/ICSI, embryo culture, and laboratory selection do not consistently generate a clinically meaningful sex-ratio shift at the embryo level when sex is genetically confirmed.

Subgroup by Genetic Era: PGT-A/NGS, Legacy Non-Day-3, and Day-3 PGD/FISH

Contemporary PGT-A/NGS/PGS cohorts (Carrasco 2022 [12], Moutos 2021 [28], Kulmann 2021 [29], Nogueira 2024 [30], Wang 2018 [31], Georgiou 2025 [32], So 2026 [33], Roberts 2018 [13], Popa 2024 [34], Liu 2019 [35], Woo 2020 [74], Zeyad 2018 [37], Cheung 2023 control arm [14], Orteiro 2021 [75]) yielded a pooled male proportion of 0.491 (95% CI 0.459–0.524), crossing 0.50. Legacy non-Day-3 studies (Alfarawati 2011 [36], ZhangRobins 2017 [41], Grunert 2015 [39], Eaton 2011 [40]) yielded a pooled proportion of 0.521 (95% CI 0.502–0.541; I^2 = 0.0%; prediction interval 0.413–0.611), narrowly excluding 0.50. Day-3 PGD/FISH studies (Kirshenbaum 2019 [44], Abotalib 2013 [38], Sindiani 2021 [24], Malpani 2002 [43], Setti 2012 [15]) yielded a pooled proportion of 0.448 (95% CI 0.372–0.526), crossing 0.50. The between-subgroup difference was statistically significant (χ^2 = 9.20, df = 2, p = 0.010), suggesting that era, platform, and embryo stage contribute to observed variation (Fig. 5).

Figure 5 *Primary subgroup analysis by genetic method and era (three pre-specified subgroups). Contemporary PGT-A/NGS/PGS blastocyst-stage cohorts (14 arms; n = 17,083): pooled proportion 0.491 (95% CI 0.459–0.524). Legacy non-Day-3 chromosomal platforms (aCGH or equivalent; 4 arms; n = 2,648): pooled proportion 0.521 (95% CI 0.502–0.541; I^2 = 0.0%; prediction interval 0.413–0.611). Day-3 PGD/FISH*

cohorts (5 arms; n = 1,730): pooled proportion 0.448 (95% CI 0.372–0.526). Between-subgroup difference: $\chi^2 = 9.20$, df = 2, p = 0.010. Random-effects HKSJ model throughout. The dashed vertical reference line is at 0.50.

Family-Balancing Cohort Subgroup

The family-balancing subgroup comprised three cohorts and 904 embryos: Kirshenbaum 2019 [44] (n = 77), Sindiani 2021 [24] (n = 585), and Malpani 2002 [43] (n = 242). The pooled male embryo proportion was 0.512 (95% CI 0.445–0.579), with $I^2 = 0.0\%$. The confidence interval included 0.50, indicating no statistically significant deviation from sex-ratio balance even within clinically enriched family-balancing programmes (Fig. 6).

Figure 6 *Family-balancing cohort subgroup analysis. Three cohorts with an explicit family-balancing or sex-selection clinical context: Kirshenbaum 2019* [44] *(n = 77; contemporary PGT-A; USA), Sindiani 2021* [24] *(n = 585; Day-3 PGD/FISH; Jordan), Malpani 2002* [43] *(n = 242; Day-3 PGD/FISH; India). Total embryos: n = 904. Random-effects logit-transformed model with HKSJ correction. Pooled male embryo proportion: 0.512 (95% CI 0.445–0.579; $I^2 = 0.0\%$; prediction interval 0.413–0.611). The confidence interval crosses 0.50, indicating no statistically significant deviation from sex-ratio balance. The dashed vertical reference line is at 0.50.*

Secondary Analysis: Comparative Meta-Analysis

Overall Secondary Analysis

The secondary comparative meta-analysis included 12 within-study comparisons from seven source papers [28, 29, 34, 35, 36, 37, 42, 73] across four domains: fertilisation method, blastulation day, TE grade, and ICM grade. The pooled odds ratio was 1.05 (95% CI 0.85–1.29; p = 0.64; $I^2 = 74.8\%$), indicating no statistically significant overall association between these non-invasive or procedural markers and embryo sex (Fig. 7).

Figure 7 *Secondary comparative meta-analysis: overall pooled odds ratio for male embryo outcome across all comparator domains. Seven source papers contributing 12 within-study comparisons across four domains: fertilisation method (IVF vs. ICSI/IMSI), blastulation day (Day 5 vs. Day 6/7), trophectoderm grade (TE-A vs. TE-B/C), and inner cell mass grade (ICM-A vs. ICM-B/C). Random-effects Mantel–Haenszel model with HKSJ correction (metabin, meta package, R v4.5.3). Male embryo = event; female embryo = non-event in all 2×2 tables. Pooled OR: 1.05 (95% CI 0.85–1.29; p = 0.64; $I^2 = 74.8\%$). The confidence interval includes 1.0, indicating no statistically significant overall association. The vertical reference line is at OR = 1.0.*

Blastulation Day (Day 5 vs Day 6/7)

Four within-study comparisons (Liu 2019 [35], Kulmann 2021 [29], Moutos 2021 [28], Zeyad 2018 [37]) contributed to this domain. The pooled estimate was not significant (OR 1.01; 95% CI 0.62–1.66; p = 0.95; $I^2 = 77.3\%$). Although individual studies have reported faster development among male embryos [12, 13], pooled evidence does not support blastulation day as a reliable sex-prediction marker.

Trophectoderm Grade (TE-A vs TE-B/C)

Four within-study comparisons (Moutos 2021 [28], Kulmann 2021 [29], Alfarawati 2011 [36], Popa 2024 [34]) contributed to this domain. The pooled estimate was not statistically significant (OR 1.20; 95% CI 0.29–4.97; p = 0.36; $I^2 = 63.5\%$), indicating that TE grade should not be used as a clinically dependable proxy for embryo sex.

Inner Cell Mass Grade (ICM-A vs ICM-B/C)

Two within-study comparisons (Moutos 2021 [28], Kulmann 2021 [29]) contributed to this domain. ICM-A embryos compared with ICM-B/C embryos yielded a non-significant pooled estimate (OR 1.01; 95% CI 0.17–5.85; p = 0.95; $I^2 = 73.8\%$), providing no evidence that ICM grade reliably predicts embryo sex (Fig. 8).

Fertilisation Method

Two within-study comparisons (Palmerola 2019 [73], Iaconelli 2010 [42]) contributed to this domain. The fertilisation-method comparison evaluated IVF versus ICSI/IMSI based on only two comparisons and produced a numerically unstable estimate (OR 1.78; 95% CI 0.00–853.39; p = 0.45; $I^2 = 83.5\%$). This estimate is computationally extreme and should not be interpreted clinically; it reflects the mathematical instability of two-study pooling with low event counts rather than a genuine biological signal. No conclusion can be drawn that IVF, ICSI, or IMSI independently alters embryo sex distribution.

Figure 8 *Secondary comparative meta-analysis by comparator domain. (A) Blastulation day (Day 5 vs. Day 6/7): pooled OR 1.01 (95% CI 0.62–1.66; p = 0.95; $I^2 = 77.3\%$). (B) Trophectoderm grade (TE-A vs. TE-B/C): pooled OR 1.20 (95% CI 0.29–4.97; p = 0.36; $I^2 = 63.5\%$). (C) Inner cell*

mass grade (ICM-A vs. ICM-B/C): pooled OR 1.01 (95% CI 0.17–5.85; p = 0.95; I² = 73.8%). (D) Fertilisation method (IVF vs. ICSI/IMSI): pooled OR 1.78 (95% CI 0.00–853.39; p = 0.45; I² = 83.5%) — based on two comparisons only; numerically unstable and not clinically interpretable. Male embryo = event; female = non-event in all 2×2 tables. The vertical reference line is at OR = 1.0.

AI and Non-Invasive Prediction: Narrative Summary

Two studies examined AI-based non-invasive sex prediction from embryo images and time-lapse data and are included in qualitative synthesis only [64, 70]. Zvereva and Dmitry [70] assessed AI embryo scoring and its relationship to sex ratio using time-lapse data; Liang et al. [64] used deep learning on time-lapse IVF movies to identify sex-linked developmental differences. AI-based embryo assessment, morphokinetic modelling, and metabolomic approaches remain prediction tools rather than diagnostic methods. Available studies are heterogeneous, often retrospective, and rarely externally validated [50, 51, 69]. These outputs should be presented to patients as research-level sex-association signals, not as family-balancing tools. PGT-A remains the only diagnostically definitive method for embryo sex identification where legally and ethically permitted [19, 20].

Discussion

Main Findings

This systematic review and meta-analysis found that post-fertilisation IVF/ICSI embryo cohorts do not show a consistent or clinically meaningful deviation from sex-ratio balance. The main pooled estimate was 0.487 (95% CI 0.463–0.512), crossing the expected 0.50 reference value. Sensitivity analyses, including leave-one-out assessment (Online Resource 2), did not materially alter this conclusion.

The secondary comparative analyses did not identify a reliable non-invasive post-fertilisation biomarker for embryo sex. Fertilisation method, TE grade, ICM grade, and blastulation day produced inconsistent findings, wide confidence intervals, and substantial heterogeneity. Kulmann [29] reported associations between day of biopsy, trophectoderm morphology, and sex proportion in PGT-A cycles, whereas Moutos [28] found no clinically decisive sex-related difference in embryo quality or transfer outcomes. The pooled evidence therefore supports counselling that morphology, timing, morphokinetics, and AI outputs cannot be used as dependable family-balancing tools.

Pre-fertilisation sperm-enrichment studies behaved differently from post-fertilisation markers. Female-selection arms showed a marked reduction in the male embryo proportion (pooled 0.21, 95% CI 0.11–0.37), whereas male-selection arms showed a higher male embryo proportion (pooled 0.70, 95% CI 0.42–0.88). Both estimates carry wide confidence intervals reflecting substantial within-group heterogeneity (I^2 = 94.2% and 96.3%, respectively), which is expected given the biological and technical diversity across flow cytometry sorting, high-magnification IMSI selection, and density gradient methods. The between-group difference remains highly significant (χ^2_1 = 23.51, df = 1, $p < 0.0001$), confirming the directional signal across all pre-fertilisation technique categories.

Pre-Fertilisation Sperm-Enrichment Methods: Available Techniques, Comparative Efficacy, and Limitations

The albumin-gradient Ericsson method was developed to exploit the hypothesised faster migration of Y-bearing sperm, but independent FISH-based evaluations have not consistently demonstrated clinically meaningful X/Y separation [8, 11]. Flow cytometry-based MicroSort® uses the approximately 2.8% DNA-content difference between X-bearing and Y-bearing spermatozoa. Karabinus [9] reported mean post-sort purities of 87.9% for X-bearing and 73.4% for Y-bearing fractions in the largest clinical programme. The ESHRE Task Force emphasised that non-medical sex selection raises ethical and safety concerns, particularly where procedures are invasive, expensive, or insufficiently validated [46].

A more recent dye-free multilayer density-gradient technique reported by Elias and colleagues [45] avoided fluorochrome and laser exposure and demonstrated embryo-level sex enrichment after ICSI with PGT-A confirmation. However, it remains a single-centre non-randomised clinical trial requiring independent multicentre replication before routine clinical adoption can be recommended. Across all pre-fertilisation methods, enrichment shifts probabilities but does not guarantee embryo sex. Definitive embryo sex identification still requires chromosomal confirmation by PGT-A or equivalent, where legally and ethically permitted [9, 45].

Strengths and Limitations

The major strength of this review is its exclusive focus on embryo-level genetic confirmation, avoiding the major bias introduced by live-birth sex or transferred-embryo sex alone. It also separates biologically distinct mechanisms: true pre-fertilisation sperm enrichment, post-fertilisation embryo-selection markers, and family-balancing cohorts.

Limitations include the predominance of retrospective designs, substantial between-study heterogeneity, non-randomised exposure allocation in comparative analyses, incomplete adjustment for maternal age and embryo cohort size, and some reconstructed counts from percentages. Several potentially relevant studies were available only as abstracts or did not provide complete raw data. The review deliberately excluded live-birth-only sex ratio data from the primary analysis, which improves embryo-level validity but limits direct inference about downstream outcomes. Formal GRADE certainty assessment was not applied; evidence certainty is rated as moderate for the primary null result and low for secondary comparative analyses, given high ROBINS-I risk of bias, substantial heterogeneity, and wide confidence intervals.

Comparison with Other Studies

The findings reconcile apparently conflicting reports in the literature. Some individual PGT-A cohorts have reported male-skewed blastocyst sex ratios, including Carrasco [12] and Georgiou [32], while other large studies, such as Nogueira [30], have reported broadly balanced euploid embryo sex ratios. Individual cohorts may be influenced by embryo stage, biopsy day, PGT platform, patient age, and selection rules, whereas the pooled estimate remains close to 50:50. The present results are also consistent with professional guidance from ASRM [47] and ESHRE [46].

Clinical and Broader Implications

This review supports a clear distinction between identifying embryo sex and influencing it. PGT-A can identify chromosomal sex among biopsied embryos where sex disclosure and use are legally and ethically permitted, but it does not create embryos of the desired sex. Intentional sperm enrichment may shift probabilities in selected settings, but it does not guarantee an outcome and is not routinely available. Non-invasive markers such as embryo grade, blastulation day, morphokinetics, and AI scores should not be marketed as dependable sex-selection tools.

Non-medical sex selection is prohibited or tightly restricted in many jurisdictions, including the UK [48] and India under the PCPNDT Act [49], and is ethically contested even where permitted. Couples seeking family balancing may pursue cross-border reproductive care, creating financial, emotional, and regulatory vulnerabilities [26]. Counselling should proactively correct common misconceptions: IVF/ICSI does not manufacture a desired sex, embryo morphology cannot reliably reveal sex, and additional cycles or medical tourism may not improve the probability of achieving the desired family composition.

Future Research

Future research should address three questions. First, can any pre-fertilisation or non-invasive post-fertilisation method predict or influence embryo sex with clinically useful accuracy? Prospective multicentre replication of the Elias sperm selection technique is a priority [45]. AI-driven embryo assessment and non-invasive PGT approaches should be evaluated with external validation, prespecified thresholds, calibration, fairness analysis, and embryo-level chromosomal reference standards [50, 51]. Second, do embryo-selection practices alter the sex ratio among transferred embryos or live births? This requires linkage between embryo-level sex, embryo-selection priority, transfer decisions, implantation, pregnancy loss, and live birth. Third, do IVF, ICSI, IMSI, or laboratory culture procedures alter the embryo sex ratio at formation or blastocyst development? Future studies should separate fertilisation-stage effects from post-fertilisation developmental selection and should report male and female counts transparently at each stage.

Conclusions

Embryo sex distribution in IVF/ICSI cohorts is broadly balanced when confirmed at the embryo level by PGT-A or equivalent chromosomal methods. Non-invasive post-fertilisation markers, including fertilisation method, TE grade, ICM grade, blastulation day, morphokinetics, and AI-based embryo assessment, show inconsistent and heterogeneous associations that are insufficient for clinical sex prediction or family balancing. Intentional sperm enrichment can shift probabilities under specific technical conditions, but it does not guarantee embryo sex and cannot be extrapolated to routine IVF/ICSI. The comparative evidence base remains limited by non-randomised design and risk of confounding, so causal claims should be avoided.

Couples seeking family balancing for non-medical reasons require clear evidence-based counselling. The expected embryo sex ratio after routine IVF/ICSI remains close to 50:50; PGT-A may reveal embryo sex where legally and ethically permitted, but does not create a desired sex; sperm enrichment may alter probabilities but remains technique-dependent and incompletely validated; and unproven sex-selection claims can lead to unnecessary cost, treatment burden, emotional distress, and cross-border care in less regulated settings.

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Figures

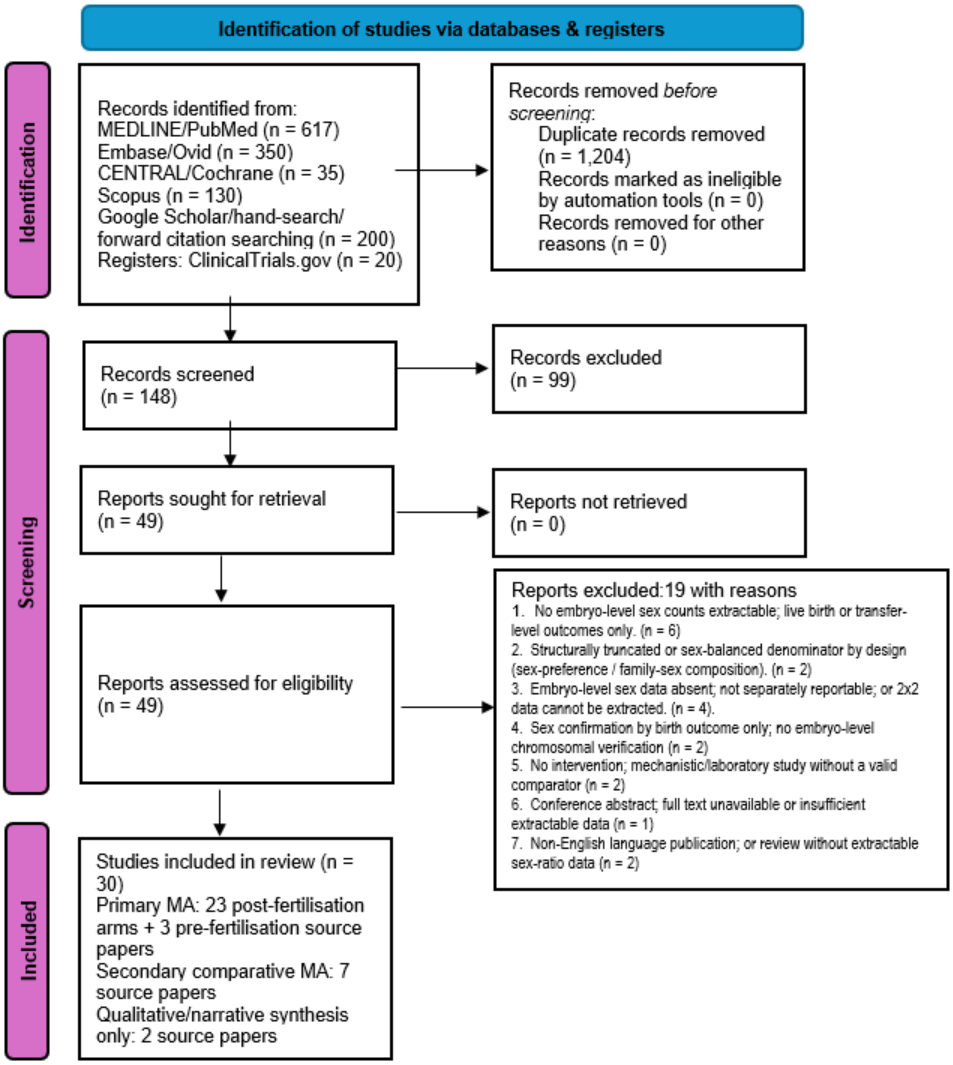


Figure 1

PRISMA 2020 flow diagram of study selection.

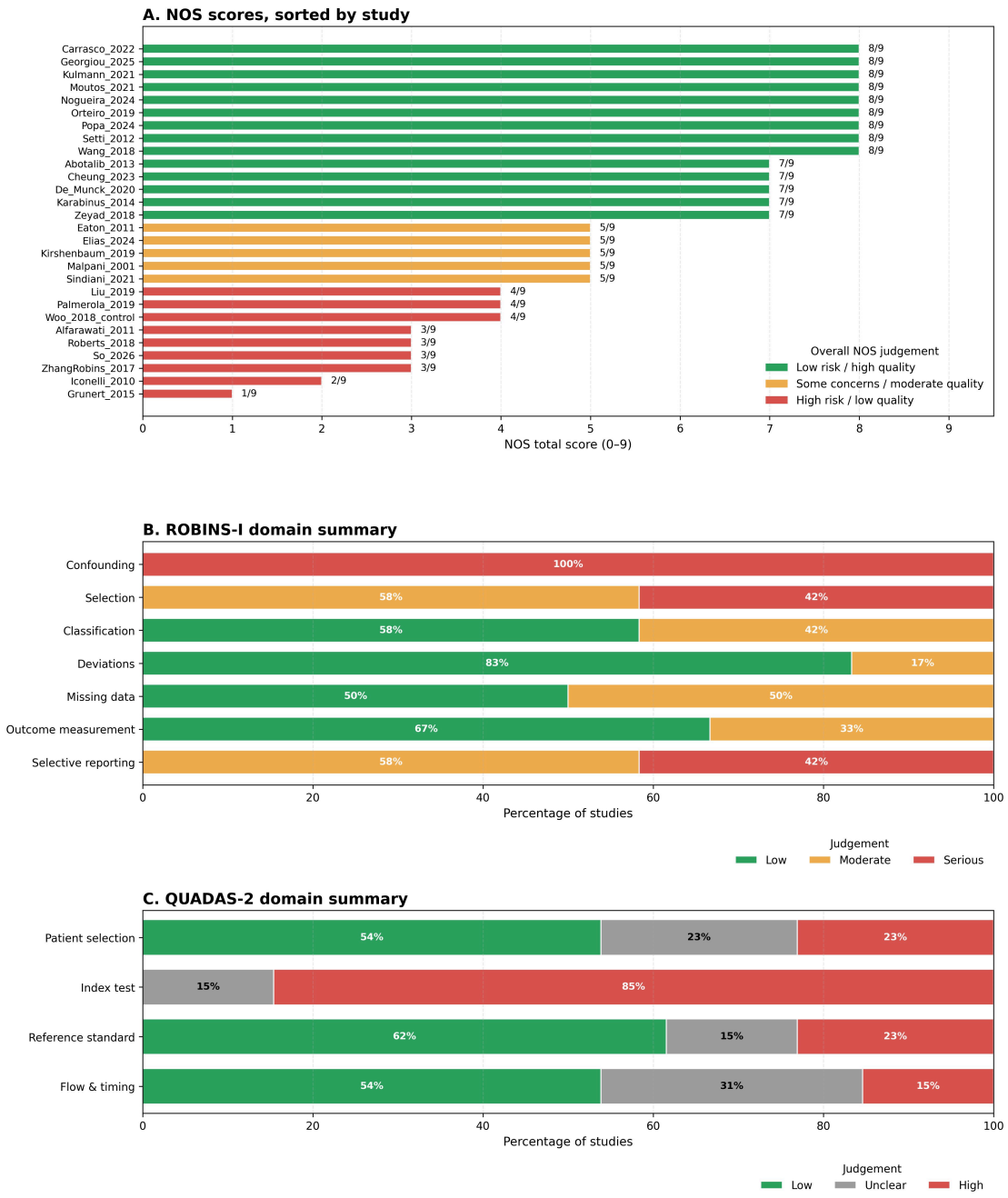


Figure 2

Integrated risk-of-bias summary. Panel A: Newcastle–Ottawa Scale (NOS) scores (0–9) for retrospective and prospective cohort studies; higher scores indicate lower risk of bias. Panel B: ROBINS-I domain-level summary for non-randomised comparative studies; domains assessed: bias due to confounding, selection of participants, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, and selection of reported results. Panel C: QUADAS-2 domain-level summary for diagnostic and predictive accuracy studies (AI-based morphokinetic models and metabolomic classifiers); domains assessed: patient selection, index test, reference standard, and flow and timing. These three tools assess different constructs and should be interpreted within-tool rather than as interchangeable scales.

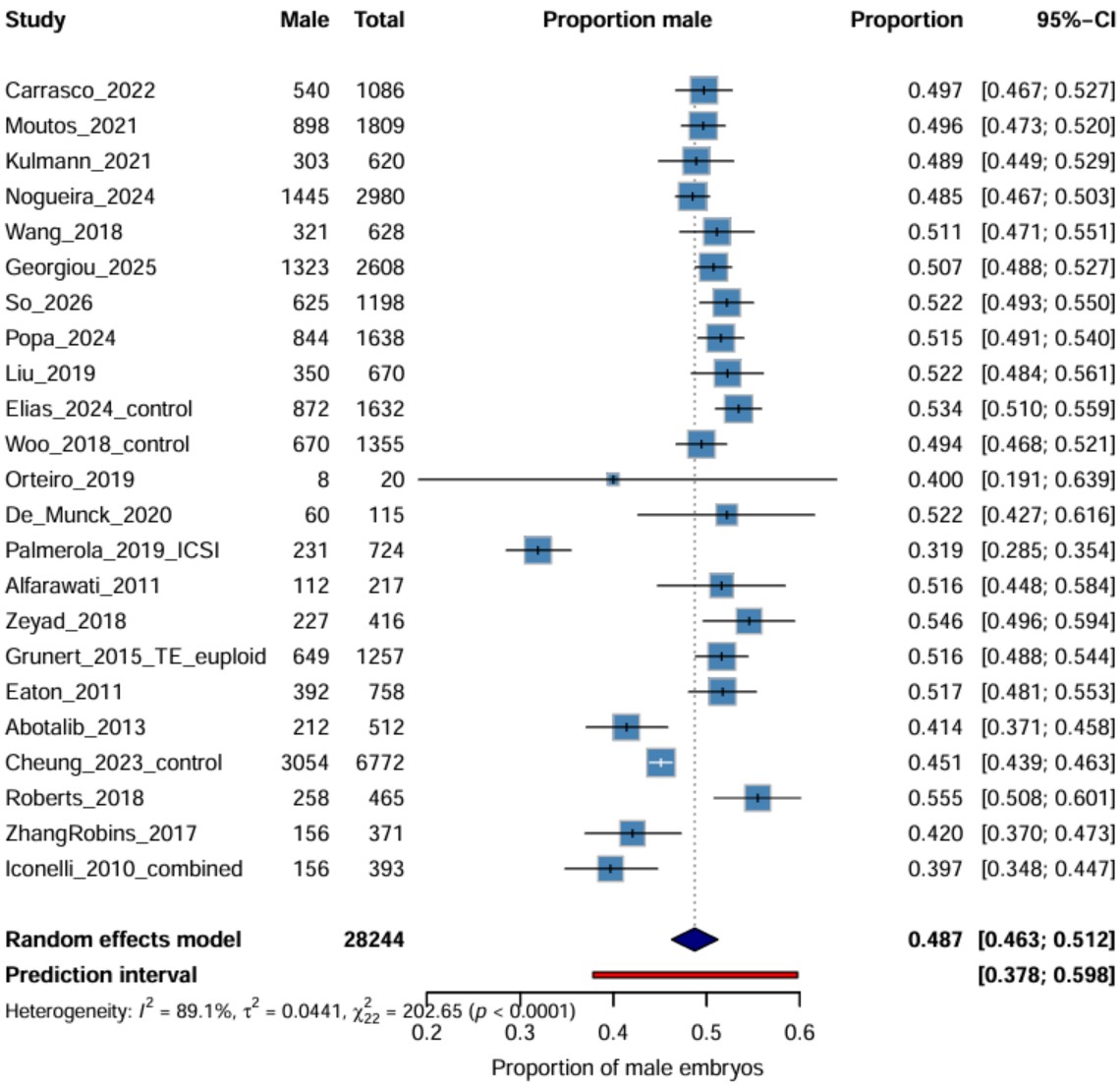


Figure 3

Primary proportional meta-analysis of post-fertilisation cohorts.

Primary proportional meta-analysis of post-fertilisation cohorts (23 analytic arms; 28,244 genetically confirmed embryos). Random-effects logit-transformed model with Hartung–Knapp–Sidik–Jonkman (HKSJ) correction (metaprop, meta package, R v4.5.3). Pooled male embryo proportion: 0.487 (95% CI 0.463–0.512). The confidence interval crosses 0.50, indicating no statistically significant deviation from sex-ratio balance. Between-study heterogeneity: I^2 = 89.1%, τ^2 = 0.0441. Prediction interval: 0.378–0.598. The dashed vertical reference line is at 0.50 (expected sex-ratio balance).

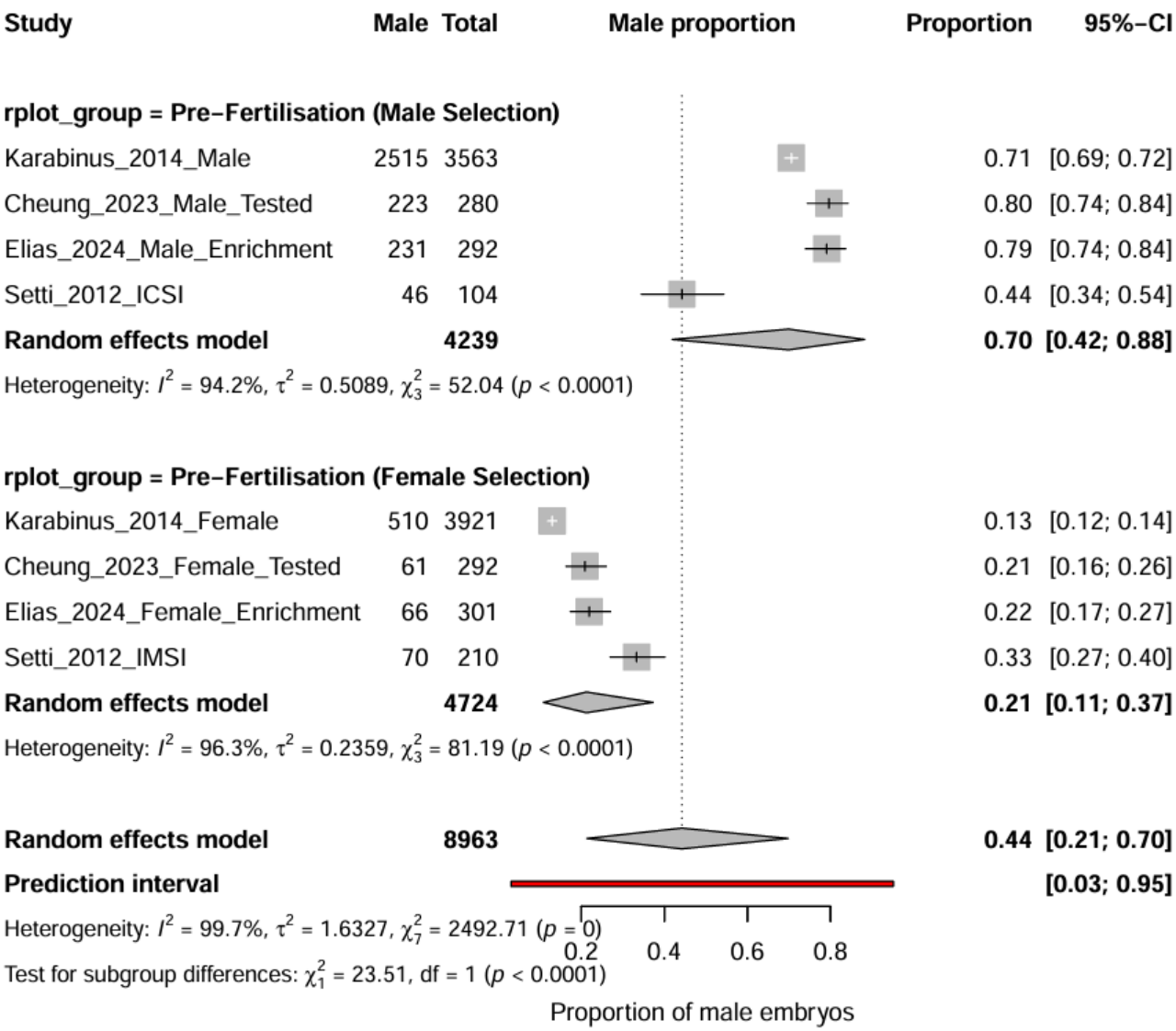


Figure 4

Pre-fertilisation categories subgroup analysis

Pre-fertilisation subgroup analysis by enrichment target (male-selection vs. female-selection arms). Eight arms from four source papers: Karabinus 2014 [9] (XSort male-target n = 3,563; YSort female-target n = 3,921); Cheung 2023 [14] (male-selection n = 280; female-selection n = 292); Elias 2022 [45] (male-enrichment n = 292; female-enrichment n = 301); Setti 2012 [15] (ICSI n = 104, male-selection comparator; IMSI n = 210, female-selection comparator). Random-effects logit-transformed model with Hartung–Knapp–Sidik–Jonkman (HKSJ) correction (metaprop, meta package, R v4.5.3). Male-selection arms (4 arms; n = 4,239): pooled male proportion 0.70 (95% CI 0.42–0.88; I^2 = 94.2%, τ^2 = 0.5089). Female-selection arms (4 arms; n = 4,724): pooled male proportion 0.21 (95% CI 0.11–0.37; I^2 = 96.3%, τ^2 = 0.2359). Between-subgroup difference: χ^2_1 = 23.51, df = 1, p < 0.0001. Overall (n = 8,963): 0.44 (95% CI 0.21–0.70); prediction interval 0.03–0.95. The dashed vertical reference line is at 0.50.

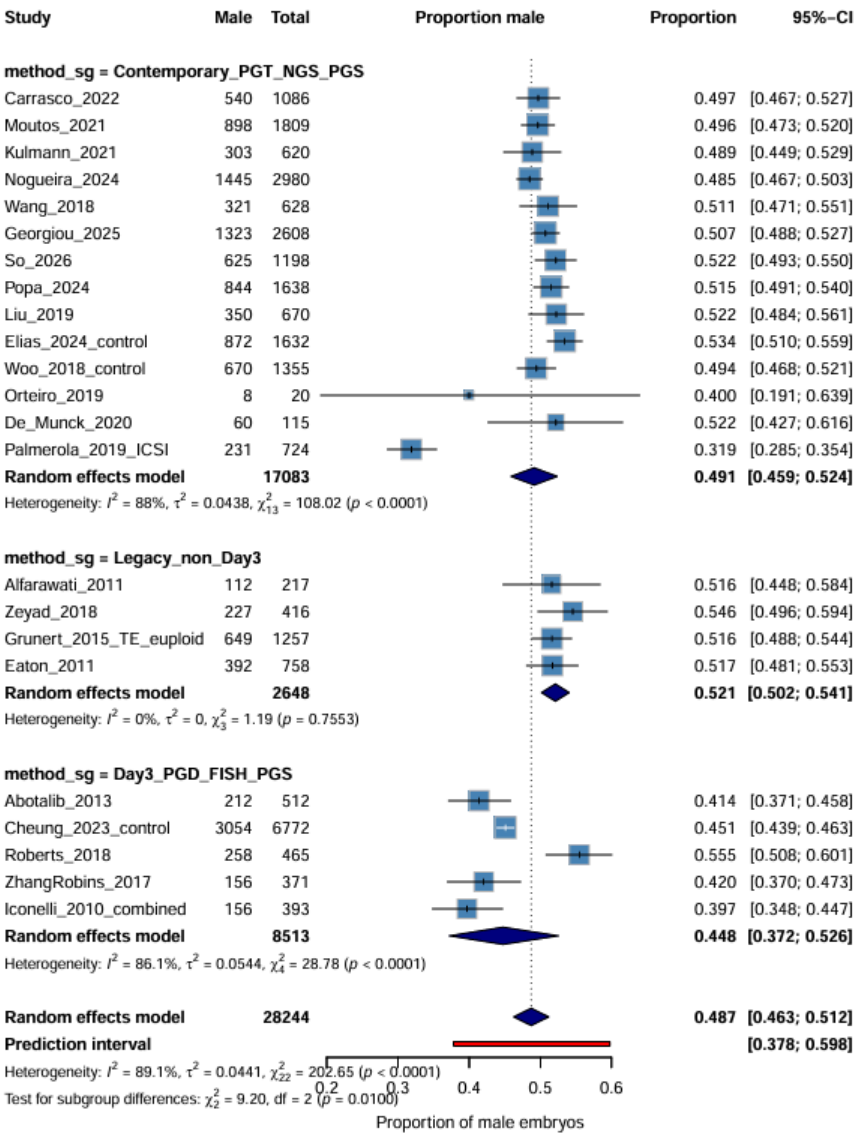


Figure 5

Primary subgroup analysis by genetic method and era

Primary subgroup analysis by genetic method and era (three pre-specified subgroups). Contemporary PGT-A/NGS/PGS blastocyst-stage cohorts (14 arms; n = 17,083): pooled proportion 0.491 (95% CI 0.459–0.524). Legacy non-Day-3 chromosomal platforms (aCGH or equivalent; 4 arms; n = 2,648): pooled proportion 0.521 (95% CI 0.502–0.541; I² = 0.0%; prediction interval 0.413–0.611). Day-3 PGD/FISH cohorts (5 arms; n = 1,730): pooled proportion 0.448 (95% CI 0.372–0.526). Between-subgroup difference: χ² = 9.20, df = 2, p = 0.010. Random-effects HKSJ model throughout. The dashed vertical reference line is at 0.50.

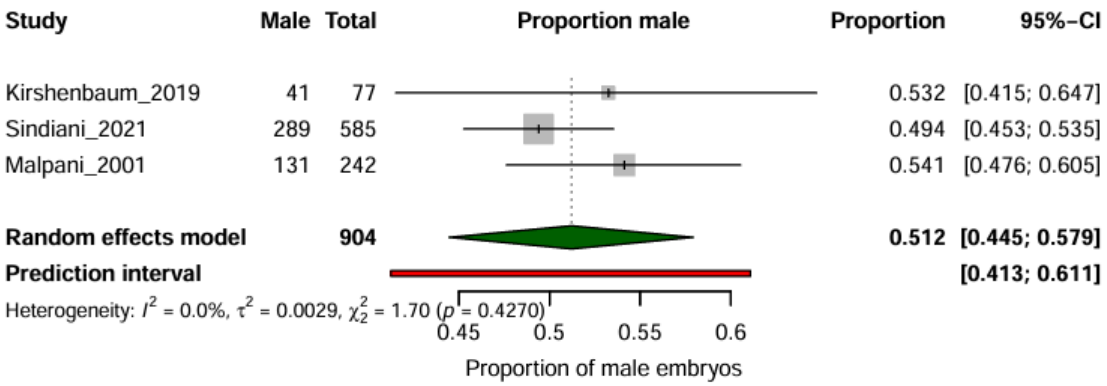


Figure 6

Family-balancing cohort subgroup

Family-balancing cohort subgroup analysis. Three cohorts with an explicit family-balancing or sex-selection clinical context: Kirshenbaum 2019 [44] (n = 77; contemporary PGT-A; USA), Sindiani 2021 [24] (n = 585; Day-3 PGD/FISH; Jordan), Malpani 2002 [43] (n = 242; Day-3 PGD/FISH; India). Total embryos: n = 904. Random-effects logit-transformed model with HKSJ correction. Pooled male embryo proportion: 0.512 (95% CI 0.445–0.579; I² = 0.0%; prediction interval 0.413–0.611). The confidence interval crosses 0.50, indicating no statistically significant deviation from sex-ratio balance. The dashed vertical reference line is at 0.50.

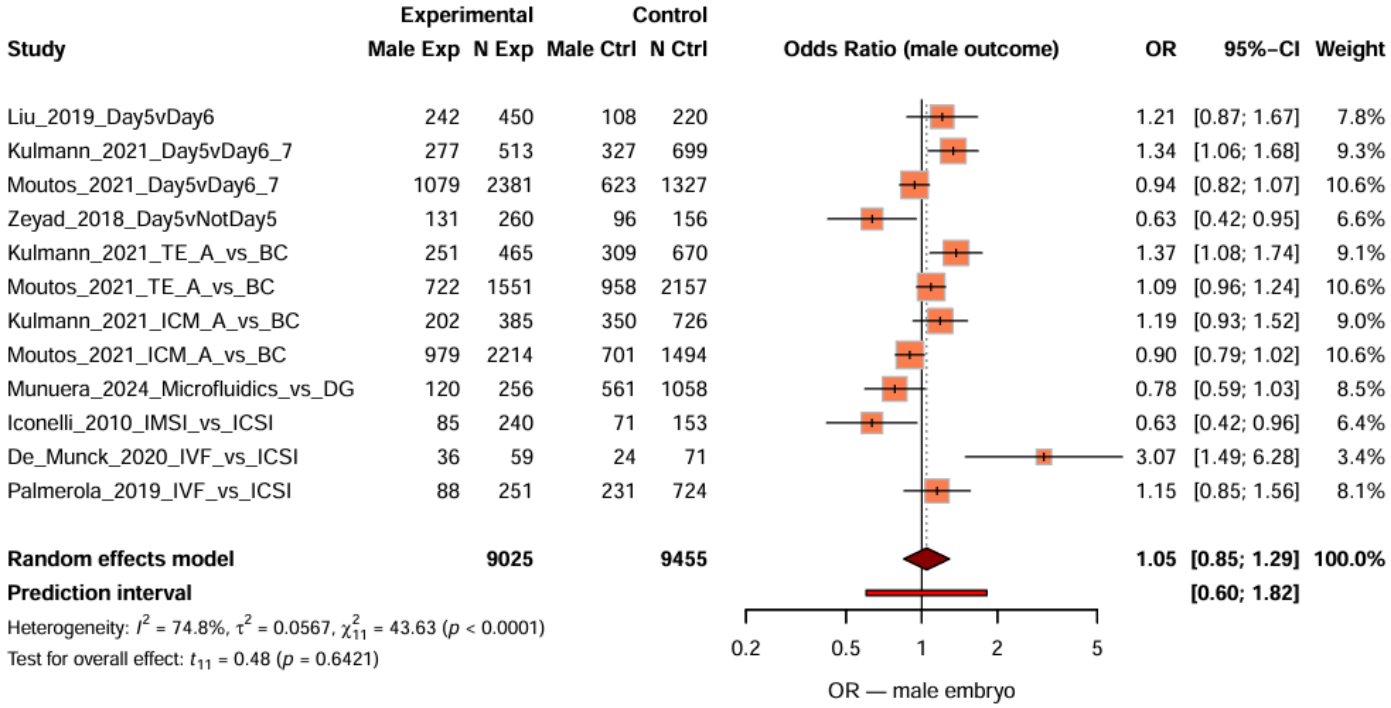


Figure 7

Secondary analysis (comparative)

Secondary comparative meta-analysis: overall pooled odds ratio for male embryo outcome across all comparator domains. Seven source papers contributing 12 within-study comparisons across four domains: fertilisation method (IVF vs. ICSI/IMSI), blastulation day (Day 5 vs. Day

6/7), trophectoderm grade (TE-A vs. TE-B/C), and inner cell mass grade (ICM-A vs. ICM-B/C). Random-effects Mantel–Haenszel model with HKSJ correction (metabin, meta package, R v4.5.3). Male embryo = event; female embryo = non-event in all 2×2 tables. Pooled OR: 1.05 (95% CI 0.85–1.29; p = 0.64; I² = 74.8%). The confidence interval includes 1.0, indicating no statistically significant overall association. The vertical reference line is at OR = 1.0.

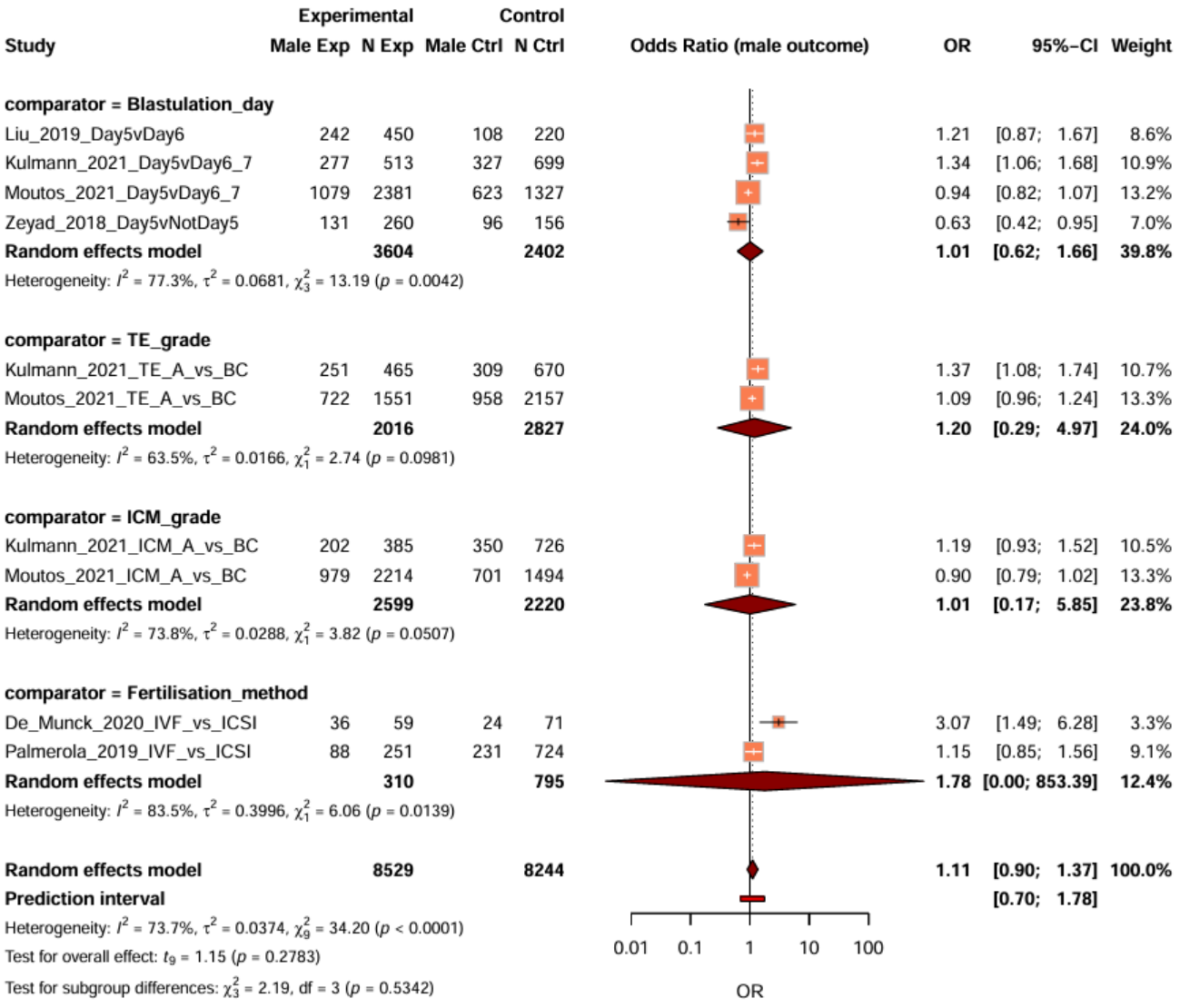


Figure 8

Secondary comparative meta-analysis by comparator domain

Secondary comparative meta-analysis by comparator domain. (A) Blastulation day (Day 5 vs. Day 6/7): pooled OR 1.01 (95% CI 0.62–1.66; p = 0.95; I² = 77.3%). (B) Trophectoderm grade (TE-A vs. TE-B/C): pooled OR 1.20 (95% CI 0.29–4.97; p = 0.36; I² = 63.5%). (C) Inner cell mass grade (ICM-A vs. ICM-B/C): pooled OR 1.01 (95% CI 0.17–5.85; p = 0.95; I² = 73.8%). (D) Fertilisation method (IVF vs. ICSI/IMSI): pooled OR 1.78 (95% CI 0.00–853.39; p = 0.45; I² = 83.5%) — based on two comparisons only; numerically unstable and not clinically interpretable. Male embryo = event; female = non-event in all 2×2 tables. The vertical reference line is at OR = 1.0.

Supplementary Files

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- SupplementaryFiguresJARG20.5.26.docx
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