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MATERNAL POLYCYSTIC OVARY SYNDROME AND OFFSPRING HEALTH PLACENTAL AND EPIGENETIC CHANGES AND METABOLIC OUTCOMES

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ABSTRACT

Maternal polycystic ovary syndrome may be associated with offspring health through metabolic, placental, and epigenetic processes; however, shared familial factors and pregnancy characteristics complicate causal interpretation. This review aimed to compare clinical outcomes and placental and epigenetic findings while distinguishing human observations from experimental results. PubMed and Europe PMC were searched on November 2, 2026. The current synthesis was based on 11 full-text reports, with three additional reports considered on the basis of their abstracts. Risk of bias was assessed for individual comparisons, and certainty of evidence was assessed by outcome. An association with obesity at ages 10–16 years, differences in birth anthropometry, and differences in lipid profiles in a selected group of girls were identified; molecular signals varied across tissues, platforms, and maternal phenotypes and did not establish a causal pathway to disease in the child. An exploratory meta-analysis of unadjusted birth weight included two cohorts comprising 291 mother–child pairs; the pooled mean difference was −106.85 g, with a 95% confidence interval from −872.19 to 658.49 g using the conservative Knapp–Hartung modification. A zero estimate of heterogeneity with two studies did not confirm homogeneity. A funnel plot and Egger's test were not used because there were too few comparable studies; the findings support individual associations and mechanistic hypotheses but do not separate the total causal effect of the syndrome from the effects of maternal obesity, gestational diabetes, infertility treatment, and other factors.

KEYWORDS: Polycystic ovary syndrome; Offspring health; Placenta; DNA methylation; Metabolic outcomes; Confounding

INTRODUCTION

Polycystic ovary syndrome (PCOS) encompasses reproductive and metabolic phenotypes that differ in androgen excess, ovulatory dysfunction, adiposity and treatment exposure. Its heterogeneity matters when offspring outcomes are examined: a physician-reported diagnosis, a clinically defined Rotterdam phenotype and a register category combining PCOS with anovulatory infertility do not necessarily represent the same exposure. International recommendations emphasize the need to consider metabolic health and pregnancy-related risks alongside reproductive manifestations (Teede et al., 2023). For offspring research, this means that diagnostic classification is part of the biological question rather than a routine descriptive variable.

The placenta represents a plausible link in maternal–fetal interactions. Features of vascular development, nutrient transport, inflammatory regulation, and lipid metabolism may accompany PCOS, whereas epigenetic differences may reflect intrauterine exposures, inherited predisposition, sample cell composition, or the subsequent environment. A change in methylation in newborn blood does not imply the same change in the placenta, and a difference in a placental transcript does not establish a persistent abnormality in the child; available studies use ultrasound imaging, transcriptomics, metabolomics, and methylation analysis, often in small subsamples relative to the entire clinical cohort (Lambertini et al., 2017; Wang et al., 2020; Polinski et al., 2023; Xie et al., 2024).

Clinical and molecular findings also occupy different positions in time. Birth size is measured at delivery; growth, circulating lipids and diagnosed obesity are assessed later. A molecular signal measured at birth may be associated with a concurrent anthropometric characteristic without predicting childhood disease. Conversely, a register association with childhood obesity provides little direct information about which placental or epigenetic pathway is involved. Establishing mediation would require temporally ordered measurements and a justified strategy for exposure–mediator, mediator–outcome and exposure–outcome confounding. None of these requirements is satisfied merely by finding enrichment of the same metabolic pathway in different datasets.

A further difficulty is separating PCOS-associated biology from maternal obesity, gestational diabetes, subfertility and its treatment. Restricting a study to assisted conceptions can improve comparability for some factors while introducing selection and leaving differences in treatment protocols unresolved. Excluding complicated pregnancies changes the target population and can remove part of the pathway being studied. These issues motivate an estimate-specific approach to bias assessment rather than a single quality label for each publication (Higgins et al., 2024).

The aim of this review was to compare clinical outcomes, placental findings and epigenetic observations in offspring exposed to maternal PCOS, to distinguish human evidence from experimental support, and to determine which estimates could reasonably be synthesized. The analysis prioritized the separation of adjusted associations from unadjusted group contrasts and treated molecular explanations as hypotheses unless a causal pathway was directly evaluated.

MATERIAL AND METHODS

Review design and information sources

This study is a critical review with a structured search and exploratory quantitative synthesis. The working protocol covered studies of maternal PCOS and offspring outcomes before age 18, including placental and molecular measures. PubMed and Europe PMC were searched in 2026. The archive contains 2353 PubMed records and 2293 Europe PMC records; after removal of 2166 duplicates, 2480 unique records remained. The main search concepts combined PCOS with offspring, childhood, newborns, cord blood, and the placenta.

Exact PubMed query: ("Polycystic Ovary Syndrome"[Mesh] OR "polycystic ovary syndrome"[tiab] OR "polycystic ovarian syndrome"[tiab] OR PCOS[tiab]) AND (offspring[tiab] OR daughter*[tiab] OR son[tiab] OR sons[tiab] OR child*[tiab] OR newborn*[tiab] OR neonat*[tiab] OR "cord blood"[tiab] OR placenta*[tiab]) AND ("1900/01/01"[Date - Publication] : "2026/11/02"[Date - Publication]).

Exact Europe PMC query: (TITLE_ABS:"polycystic ovary syndrome" OR TITLE_ABS:"polycystic ovarian syndrome" OR TITLE_ABS:PCOS) AND (TITLE_ABS:offspring OR TITLE_ABS:daughter* OR TITLE_ABS:son OR TITLE_ABS:sons OR TITLE_ABS:child* OR TITLE_ABS:newborn* OR TITLE_ABS:neonat* OR TITLE_ABS:"cord blood" OR TITLE_ABS:placenta*) AND FIRST_PDATE:[1900-01-01 TO 2026-11-02]. Neither query required a separate molecular term.

At the time of synthesis, screening of 73 unique records had been documented: seven were excluded and 66 were referred for full-text assessment; of 13 full reports assessed, two were excluded and 11 provisionally met the criteria. There remained 53 unresolved full-text decisions and 2407 records at the first screening stage; these numbers describe the status of selection on the analysis date. Three additional abstract-only reports were not added to the 11 full-text reports as fully assessed studies.

Eligibility extraction and cohort linkage

Eligible human contrasts compared offspring or pregnancy-related specimens from mothers with PCOS and an appropriate non-PCOS reference group. A treatment comparison among women with PCOS was distinguished from the maternal exposure contrast. Thus, a cohort drawn from a placebo arm of a randomized trial did not make its comparison with an external population randomized. Adult-only offspring effects were not treated as pediatric estimates. Secondary reviews were used for context and reference checking rather than counted as independent primary cohorts.

Extraction covered design, setting, recruitment period, diagnostic criteria, maternal and offspring characteristics, clinical and analytical sample sizes, tissue, laboratory platform, outcome definition, effect scale, confidence interval and adjustment variables. Means, standard deviations, standard errors and medians were kept distinct. Published and calculated intervals were labeled separately. For each possible overlap, the center, recruitment years, cohort name, treatment context and age at follow-up were compared. Uncertain independence was retained as uncertainty rather than resolved by assuming that different publications contained different participants. Data extraction and appraisal were not independently duplicated by two human reviewers.

The synthesis retained separate clinical, placental and epigenetic streams and a distinct experimental stream. Table 1 defines their boundaries; it also prevents tissue-specific molecular results from being interpreted as interchangeable clinical outcomes.

Table 1. Synthesis streams and limits of interpretation

Stream	Evidence examined	Interpretation
Human clinical outcomes	Birth anthropometry, growth, obesity diagnoses and lipid measurements; 11 full-text reports and three additional abstract-level reports across the review.	Adjusted associations were separated from raw means. Age strata from one cohort were not counted as independent studies.
Human placental findings	Ultrasound volume and vascular measures, RNA/protein expression and metabolites in placenta and related fluids.	Morphometry, transcripts and metabolites represented distinct outcomes. Amniotic fluid was not classified as placental tissue.

Human epigenetic findings	DNA methylation in neonatal blood spots, cord blood and placenta; additional infant blood data.	Numbers of CpGs or differentially methylated regions were not effect sizes. Methylation was not equated with expression or disease risk.
Animals and cells	The separable rat and Swan71 cell components of Wang et al. (2020).	Supportive mechanistic comparison. No full independent animal search, SYRCLE appraisal, or animal meta-analysis was performed.

The target interpretation was an association with maternal PCOS that could not automatically be attributed to obesity, diabetes or fertility treatment. Before judging adjustment, the timing and possible causal role of each covariate were considered. Maternal body mass index (BMI) before conception, BMI at an early pregnancy visit and a register diagnosis of obesity were not treated as equivalent measurements. Gestational diabetes, gestational weight gain, treatment after diagnosis and gestational duration could lie downstream of the exposure, depending on the causal question. Adjustment for these variables was not automatically considered superior control of confounding. Table 2 summarizes how this principle was applied.

Table 2. Maternal factors and the meaning of statistical adjustments

Factor	**Interpretive question**	**Application**
Adiposity and metabolic health	We distinguish measured preconception BMI, BMI at an early visit, and a register diagnosis of obesity. Familial predisposition is considered; the absence of a significant baseline BMI difference does not prove the absence of confounding.	Talmo: models without and with BMI are presented separately. Chen: the main analysis lacks measured BMI for the entire period, so independence from maternal obesity has not been established (Talmo et al., 2024; Chen et al., 2021).
Gestational diabetes	May lie on the pathway from the maternal metabolic phenotype to the outcome. Adjustment for and exclusion of GDM are assessed separately from control of baseline confounders; timing of diagnosis and treatment are recorded.	Exclusion of complicated pregnancies in Ge narrows applicability. The difference in GDM frequency in Wu X requires caution; its contribution cannot be considered eliminated through group comparison or BMI matching (Ge et al., 2025; Ge et al., 2026; Wu et al., 2026b).
Infertility and treatment	Separate subfertility, ovulation induction, IVF/ICSI, embryo transfer and drug exposure. Treatment may follow PCOS diagnosis, while conditioning on assisted conception can alter the comparison.	Lambertini and Wu X examine selected ART groups; this does not eliminate all treatment differences. In Berns, the conclusion depends on control fertility; in Wu S, treatment and twins are distributed asymmetrically.
Other covariates and selection	Consider age, parity, smoking, social factors, child sex/age, plurality and family environment. Justify adjustment for gestational age, weight gain and cell composition.	Adjustment for gestational age at delivery and weight gain may change the target estimate. Technical omics adjustments do not replace clinical confounding control; single-sex and cesarean-only samples limit generalizability.

IVF, in vitro fertilization; ICSI, intracytoplasmic sperm injection. Applications refer to Lambertini et al. (2017), Chen et al. (2021), Talmo et al. (2024), Berns et al. (2025), Ge et al. (2025, 2026) and Wu et al. (2026a, 2026b).

The Risk Of Bias In Non-randomized Studies of Exposures framework (ROBINS-E, March 24, 2024 version) informed seven-domain judgments for eight specified exposure contrasts (Higgins et al., 2024). Two further unadjusted molecular contrasts were stopped at the initial screening stage because of very high concern about confounding. A cross-sectional offspring lipid comparison was appraised separately with the analytical cross-sectional checklist (JBI, 2017). Domain judgments were based on available reports and should not be described as ten fully completed official signaling-question forms. No composite numerical quality score was calculated.

RoB 2 was reserved for randomized treatment effects and ROBINS-I for nonrandomized intervention effects. Neither was applied to an observational PCOS contrast merely because participants originated from a trial. AMSTAR-2 was relevant to secondary systematic reviews rather than to primary exposure studies and was not used to score this primary evidence set. Experimental animal findings were described without assigning an unperformed SYRCLE assessment. Certainty was considered separately for individual outcomes using the traditional GRADE approach, with observational evidence starting at low certainty and further reductions tied to specific limitations rather than to nonrandomization alone (Guyatt et al., 2011).

Pooling required an interpretable common outcome, compatible units and timing, sufficient dispersion data and no known participant overlap. Adjusted effects with materially different covariate structures were not pooled automatically. Hazard ratios were not combined with mean differences, standardized birth-size scores were not combined with grams, and medians were not substituted for means. No common molecular effect was constructed from different genes, metabolites, tissues or pathway annotations.

A post hoc exploratory analysis was restricted to unadjusted birth weight among singleton girls delivered by cesarean section in Wang et al. (2020) and Xie et al. (2024). Their recruitment periods at the same Zhejiang center did not overlap, although individual identifiers were unavailable. The effect was the mean difference in grams, PCOS minus control. In

Wang, standard errors of the mean were converted to standard deviations using SD = SEM × √n after conversion from kilograms to grams. Within-study variance was $SD^2PCOS/nPCOS + SD^2control/ncontrol$. Random-effects variance was estimated by restricted maximum likelihood. A modified Knapp–Hartung interval used $q^* = \max(1, q)$ and a t distribution with $k - 1$ degrees of freedom; a normal-approximation interval was a sensitivity analysis (Bender et al., 2018).
Heterogeneity was described using Cochran's Q, I^2, and τ^2, taking their instability at $k = 2$ into account. Sequential exclusion of studies left one study and was interpreted descriptively; a prediction interval, meta-regression, and subgroup meta-analysis were not calculated. A funnel plot and Egger's test required at least ten independent comparable studies of a single outcome and sufficient variation in precision. The total number of reports across different outcomes did not meet this condition (Page et al., Cochrane Handbook, Chapter 13).

RESULTS

The 11 full-text reports ranged from population-based follow-up to small molecular comparisons at delivery. Most clinically defined PCOS cohorts used Rotterdam criteria, while Upstate KIDS relied on maternal report of a physician diagnosis and the Finnish register study combined PCOS and anovulatory infertility. Analytical subsets were frequently much smaller than the clinical cohorts. Table 3 presents the population and assay structure to make these differences visible before comparing outcomes.

Table 3. Characteristics of primary reports and analytical samples

Report	Population and PCOS definition	Material and analysis
Polinski 2023	Upstate KIDS, USA; 849 pairs: 102 PCOS (33 with hirsutism) and 747 controls. Physician diagnosis reported postpartum.	Neonatal dried blood spots; EPIC methylation array; cell-composition and batch adjustment.
Lambertini 2017	Mount Sinai; six PCOS and six controls; all IVF, term singleton births; Rotterdam criteria.	Cord blood; HumanMethylation450; laboratory blinding; incomplete control of clinical and cellular differences.
Wang 2020	Zhejiang, June 2016–June 2017; 20 PCOS and 32 controls; singleton girls, cesarean; Rotterdam.	Placental RRBS/RNA-seq 3 + 3; qPCR in a larger sample; cord serum; rats and cells considered separately.
Xie 2024	Zhejiang, June 2019–June 2020; 103 PCOS and 136 controls; singleton girls, cesarean; Rotterdam.	Fetal side of the placenta; RNA-seq 5 + 5; ceRNA network and qPCR.
Ge 2025	Chengdu; 45 PCOS and 50 controls; Rotterdam; uncomplicated elective cesarean pregnancies.	Placental maternal surface and cord serum; gas chromatography–mass spectrometry. Recruitment dates not clearly stated.
Ge 2026	Same Chengdu center, January 2020–December 2021; 48 PCOS and 50 controls; Rotterdam.	Metabolomics/lipidomics; adjustment included age, early-pregnancy BMI, gestation and gestational weight gain.
Wu S 2026	Jiangsu, September 2023–December 2025; 25 + 25 recruited, 22 + 23 after quality control; Rotterdam.	Amniotic fluid, LC-MS/MS; placental RNA-seq 8 + 6; independent qPCR 4 + 4.
Berns 2025	Rotterdam Predict/VIRTUAL Placenta; 41 PCOS, 63 subfertile and 102 fertile controls.	Serial ultrasound placental volume, vascular volume and Doppler; no molecular assay.
Wu X 2026	Zhejiang assisted-reproduction follow-up; 40 exposed and 40 control girls aged 4–6 years; maternal Rotterdam PCOS.	Child serum metabolomics and Olink Target 96 Cardiovascular III; cross-sectional clinical comparison.
Talmo 2024	390 PCOS pregnancies from the placebo arms of three RCTs versus 68 708 MoBa pregnancies; Rotterdam.	Birth anthropometry and placental mass; external observational comparison rather than a randomized exposure.
Chen 2021	Finnish births in 1996–2014, follow-up through 2018; 1 097 753 children, 24 682 with maternal PCOS/anovulatory infertility.	Register diagnoses of offspring obesity/diabetes; maternal diagnosis timing and incomplete measured BMI limited interpretation.

RRBS, reduced representation bisulfite sequencing; qPCR, quantitative polymerase chain reaction. Counts are clinical samples unless a smaller analytical subset is specified. Wu S and Wu X correspond to Wu et al. (2026a) and Wu et al. (2026b), respectively.

Publication counts exceeded the number of clearly independent cohorts. Polinski (2023), Bell (2018) and Polinski (2024) arose from Upstate KIDS and were linked as related reports, not three independent replications. The two Ge reports originated from the same Chengdu center, and participant overlap remained unresolved. The 2025 correction to Ge concerned figure legends and did not create a new cohort. Berns used the same 41 PCOS pregnancies against two reference groups; the larger Predict analysis likewise did not constitute external replication. Wang and Xie had nonoverlapping delivery periods, supporting their use in the restricted exploratory analysis, whereas possible overlap between earlier Zhejiang births and the later child follow-up could not be resolved from available identifiers.

Clinical outcomes in human offspring

Birth anthropometry, early growth, and subsequent metabolic measures did not constitute a single phenotype. Table 4 considers the estimates in relation to age, exposure definition, and control group.

Table 4. Clinical findings and limitations

Outcome	Reported findings	Comparison and interpretation
Birth size	Talmo 2024: birth-weight z-score MD −0.26 (95% CI −0.38…−0.14) without BMI and −0.39 (−0.51…−0.27) with BMI. In Wang 2020 and Xie 2024, raw mean weights are also lower, but the estimates are imprecise (Wang et al., 2020; Xie et al., 2024; Talmo et al., 2024).	Talmo provides an adjusted standardized contrast; the other studies provide raw means. Pooling these into one effect would mix different causal questions. Accounting for BMI changes the estimate but does not establish a mechanism.
Early growth	Bell 2018, Upstate KIDS: differences through age 3 in weight, 4.81 g (−95.1…104.7), height, 0.18 cm (−0.16…0.52), and BMI, −0.14 kg/m² (−0.30…0.01); abstract information (Bell et al., 2018).	No clear early-growth difference was demonstrated. Intervals crossing zero did not establish equivalence; full-text assessment remained incomplete.
Childhood obesity	Chen 2021: HR 1.37 (1.19–1.57) at ages 10–16; the separate ≤9-year stratum has HR 1.58 with a published CI of 1.30–1.81 (Chen et al., 2021).	The exposure includes anovulatory infertility; maternal diagnosis is considered regardless of the year it was established. The main model lacks measured BMI for the entire period. The two age-specific effects cannot be counted as two independent studies.
Lipid profile	Wu X 2026: in girls aged 4–6 years, TC was 4.69 versus 3.91 and LDL-C was 2.76 versus 2.21 mmol/L; HDL-C was also higher. BMI and glycemic measures did not differ significantly (Wu et al., 2026b).	Selected girls after assisted reproduction; an altered profile was observed, not future cardiovascular disease. Higher HDL was not automatically classified as adverse.
Measures near age 9	Polinski 2024, Upstate KIDS: the abstract reports no differences in blood pressure, arterial stiffness, lipids, HbA1c, or anthropometry (Polinski et al., 2024).	Different age and sampling from Wu X; significance alone did not establish disagreement. Abstract-level evidence was not treated as a complete null-effect estimate.

CI, confidence interval; HR, hazard ratio; LDL/HDL, low-/high-density lipoprotein. Sources: Bell et al. (2018), Chen et al. (2021), Talmo et al. (2024), Polinski et al. (2024) and Wu et al. (2026b).

The Finnish register result provided the clearest later childhood clinical association in the current full-text set, but its scale did not compensate for exposure ambiguity. Maternal diagnoses were not restricted to those established before the index birth, and the main adjustment relied on obesity diagnoses rather than measured BMI across all years. The association therefore could not be described as a pure intrauterine effect independent of adiposity or family environment (Chen et al., 2021). The 17–22-year age stratum was not used to characterize pediatric outcomes.

In the assisted-reproduction follow-up of girls aged 4–6 years, lipid differences were contemporaneous measurements. The reported area under the receiver operating characteristic curve of 0.93 (95% CI 0.88–0.98) concerned discrimination of hyperlipidemia within the analyzed setting; it was not prospective validation of cardiovascular disease prediction. Differences in gestational diabetes and selective participation remained relevant despite parental matching. The findings did not establish that children of mothers with PCOS inevitably develop metabolic disease (Wu et al., 2026b).

Placental findings differed by the timing and nature of measurement (Table 5). In early pregnancy, the ultrasound contrast depended on whether PCOS pregnancies were compared with subfertile or fertile controls. At delivery, placental mass represented a different outcome and could not be merged with first-trimester volume by merely standardizing the measurements.

Table 5. Placental and maternal–fetal findings

Component	Observation	Meaning and limitation
Volume and vascular development	Berns 2025: PV at 11 weeks is lower versus subfertile controls, β −0.286 (−0.419…−0.152) on the cube-root cm³ scale. Versus fertile controls: −0.056 (−0.164…0.053), model 2 (Berns et al., 2025).	Reference-group dependence; both contrasts shared 41 PCOS pregnancies. Additional Predict analyses were not independent replication.
Placental mass	Talmo 2024: the model including BMI, gestational age, and sex gives MD −25 g (−43…−6) (Talmo et al., 2024).	Different measurement and gestational window from ultrasound volume; a pooled standardized difference would obscure biological meaning.
Trophoblast and neurotrophins	Wang 2020: reduced FOS/NGF, evidence of changes in the vascular bed and transport proteins; lower cord-blood BDNF/NGF (Wang	Human comparisons were observational, with some assays limited to 3 + 3 or 5 + 5. Cell manipulation supported expression regulation

	et al., 2020).	without proving a child disease pathway.
Immune-related expression	Xie 2024: the ceRNA network includes 29 lncRNAs, 13 miRNAs, 18 mRNAs, and 57 events; RNA-seq in only 5 + 5 of 239 participants (Xie et al., 2024).	The network results from computational selection. It does not represent 57 independently validated mechanisms; the clinical sample does not replace the omics analysis sample size.
Placental and cord-serum metabolites	Ge 2025: 79 and 25 significant metabolites, respectively; Ge 2026 adds lipidomics and associations with testosterone (Ge et al., 2025; Ge et al., 2026).	Pathway-level comparison generated hypotheses. Possible Chengdu overlap precluded treating repeated pathway annotations as independent replication.
Amniotic lipids	Wu S 2026: PC/PE 0.62 versus 1.15. PE(16:0/20:4) is associated with child weight: r −0.376 (bootstrap CI −0.625…−0.066); adjusted β −174.37 g (−337.48…−11.25) (Wu et al., 2026a).	A lipid–birth-weight association was not the effect of PCOS on birth weight. Several associations attenuated after adjustment; mediation was not estimated. Separate placental qPCR 4 + 4 supplied limited tissue comparison.

Sources: Wang et al. (2020), Xie et al. (2024), Talmo et al. (2024), Berns et al. (2025), Ge et al. (2025, 2026) and Wu et al. (2026a). PC and PE denote phosphatidylcholine and phosphatidylethanolamine. β coefficients retain their original scales. FOS/NGF expression is distinguished from circulating neurotrophin protein.

The amniotic-fluid analysis illustrates the need to distinguish exposure contrasts from biomarker associations. Four twin pregnancies occurred only in the PCOS group, and fertility treatment also differed by group. The reported lipid–birth-weight regression included PCOS, gestation, infant sex and fetal number, but this did not estimate a mediated effect of maternal PCOS. A second lipid, PC(P–18:0/18:1), had an adjusted coefficient of −216.32 g (95% CI −404.96 to −27.68). These coefficients were not pooled with the raw PCOS–control birth-weight differences. In the source report, the PC/PE ratio and PE correlation appeared in Figure 8b–c, adjusted lipid associations in Figure 9 and placental sequencing/qPCR in Figure 10 (Wu et al., 2026a).

The Ge studies were compatible with altered maternal–fetal metabolic communication, but the overlap question and exclusion of complicated pregnancies constrained interpretation. Adjustment in the 2026 report included gestational duration and gestational weight gain alongside age and early-pregnancy BMI. Such modeling could change the target effect by conditioning on consequences of maternal phenotype. It did not by itself separate an androgen-mediated pathway from all obesity-related influences (Ge et al., 2025, 2026). The correction to the 2025 report concerned Figure 3 legends, not a new cohort (Correction to: Metabolic profiles of pregnancy with polycystic ovary syndrome, 2025).

Epigenetic findings

The epigenetic results were tissue- and phenotype-specific (Table 6). The strongest adjusted neonatal analysis distinguished PCOS with and without hirsutism, whereas the smallest pilot study compared only 12 cord-blood samples. Differences in signal counts were therefore not a measure of stronger or weaker biological effects.

Table 6. Human epigenetic findings

Report and specimen	**Principal finding**	**Comparability**
Polinski 2023; neonatal dried blood spots	PCOS with hirsutism: 3 CpGs after FDR correction and 8 DMRs. cg02372539 β −0.0807 (SE 0.010), cg08471713 β 0.0773 (SE 0.014), cg17897916 β 0.0501 (SE 0.009). Without hirsutism, there are no significant individual CpGs in the main analysis (Polinski et al., 2023).	Adjustment included cell composition, batch and maternal characteristics. EAGeR tested testosterone in women without PCOS and was not an independent replication of maternal PCOS.
Lambertini 2017; cord blood	6 + 6 after IVF; 614 hypermethylated and 1066 hypomethylated CpGs, annotated to, among others, 918 unique genes (Lambertini et al., 2017).	450K platform and different specimen/analytical control. CpG counts were not combined with region counts or locus-specific β values; shared gene annotation did not establish the same locus.
Wang 2020; placenta	RRBS/RNA-seq 3 + 3; global promoter/expression differences. Targeted testing of BDNF, NGF, and FOS promoters found no significant methylation differences (Wang et al., 2020).	Lower expression was not explained as proven methylation of these same promoters. The targeted null findings were retained.
Echiburú 2020; infant blood at 2–3 months	24 + 24, half of the PCOS mothers received metformin. The abstract describes sex differences in LEP/LEPR, ADIPOR2, AMH, and AR methylation (Echiburú et al., 2020).	Abstract-only supplementary evidence. Sex and treatment were kept distinct; full-text appraisal and quantitative pooling were not completed.

β represents the reported methylation coefficient rather than a disease risk estimate. Gene symbols refer to the loci examined; no shared causal pathway is inferred from annotation.

No extractable pair of independent cohorts provided the same CpG effect in the same tissue, age window and maternal phenotype with compatible scale and variance. A methylation meta-analysis was therefore not performed. In Polinski et al. (2023), the fully adjusted model included maternal age, BMI, parity, race, education, assisted reproduction, cell composition, batch and ancestry-related factors. This was stronger confounding control than simple baseline group comparisons but still did not isolate an exclusively intrauterine effect from inherited or shared familial determinants.

The placental neurotrophin study was especially informative about the limits of mechanistic wording. Expression and circulating protein differences coexisted with nonsignificant targeted promoter methylation results. Describing the lower neurotrophin concentrations as caused by methylation of BDNF, NGF or FOS would contradict the target-specific findings. More generally, pathway enrichment across methylation and expression datasets did not establish mediation or clinically relevant persistence into childhood (Wang et al., 2020).

Only the separable experimental components of Wang et al. (2020) were considered here. Their results were kept outside the human effect estimates and did not constitute an independent systematic animal review (Table 7).

Table 7. Experimental findings and transferability to humans

Model	Design and result	Permissible inference
Maternal rat phenotype	20 female Sprague–Dawley rats were initially allocated 10 per group; testosterone propionate on postnatal day 9 versus oil. Animals with disturbed cycles were selected for subsequent experiments; the model was confirmed hormonally and morphologically.	The induced phenotype represented selected PCOS features, not the full human syndrome. Selection after induction affected interpretation.
Female F1 offspring	Morris water maze at 5 weeks: 5 model animals and 7 controls, fewer target crossings. At 13 weeks: 6 + 6, no significant differences; Figure 5.	Age-specific finding; no generalization to all learning measures, all ages or obesity. A later nonsignificant contrast did not establish recovery without an age interaction analysis.
Female F2 offspring	At 5 and 13 weeks, 6 + 6; no significant differences in the described test.	Persistent second-generation impairment was not demonstrated. Generations were not treated as independent experiments for pooling.
F1 brain tissue	Transcript and ultrastructural changes in hippocampus/hypothalamus described around puberty.	Consistency within a model supported a hypothesis, not causality of a placental marker in humans.
Swan71 cells	Stable FOS overexpression: NGF expression increased and BDNF decreased; experimental comparisons used 3 replicates in the indicated panels.	An intervention in cultured cells was separate from maternal exposure contrasts and animal behavior. Cell replicates were not numbers of mothers or children.

Source: Wang et al. (2020). Independent litters, allocation concealment and blinding were not sufficiently verified for a low-risk experimental designation. Animal numbers were not assumed to equal independent maternal/litter units.

The neonatal androgen exposure used to induce the maternal phenotype preceded the pregnancies under study and should not be conflated with a measured gestational androgen exposure in humans. Behavioral differences in one age window could support investigation of neurodevelopmental regulation, but they supplied no direct estimate of offspring metabolic disease. The null adult and F2 findings were retained rather than omitted from a proposed multigenerational mechanism.

Only one restricted clinical contrast supported an exploratory quantitative analysis. The remaining outcomes failed compatibility or independence checks for the reasons in Table 8. This decision was based on the meaning of the estimates before examining heterogeneity statistics.

Table 8. Decisions on quantitative pooling

Outcome	Compatibility assessment	Decision
Birth weight in grams	Wang 2020 and Xie 2024: Rotterdam, one center, different periods of 2016–2017 and 2019–2020, singleton girls delivered by cesarean section, means and variances available.	Exploratory raw mean-difference analysis. Individual identifiers were unverified; one-center recruitment limited external replication.
Adjusted anthropometry	Talmo reported z scores and alternative models; Ge reported medians; Wu S included twins and asymmetric assisted-conception exposure.	No main adjusted pool. Medians were not converted to means, z scores were not combined with grams and Talmo models were not duplicated.
Childhood obesity	One register cohort with age-stratified HRs and a combined exposure.	No independent comparable pool; HRs for ≤9 and 10–16 years were not pooled as independent studies.
Childhood lipids	Wu X: girls aged 4–6 after assisted reproduction. Polinski: around age 9, both sexes; full compatible effect not extracted.	Narrative comparison; no compatible adjusted age-/sex-specific estimates.
Placental volume	One early-volume study and a different birth-	Not pooled across measurement or timing;

and mass	mass study.	Berns controls shared cases.
Genes metabolites and CpGs	Different tissues, platforms, targets, subsets and covariates; unresolved Chengdu overlap.	No common molecular effect or quantitative pool.
Animal outcomes	One separable experimental complex with dependent ages and generations.	No animal meta-analysis.

The two cohorts contributed 291 mother–infant pairs. Individual mean differences and reconstructed standard deviations are reported in Table 9. These were unadjusted descriptive contrasts within a selected birth population, not identified causal effects of PCOS.

Table 9. Source data for the exploratory birth-weight analysis

Report	PCOS n; mean; SD, g	Control n; mean; SD, g	Calculated MD and 95% CI, g
Wang 2020	20; 3370; 402.49	32; 3560; 395.98	−190.00 (−413.47…33.47)
Xie 2024	103; 3246.96; 592.73	136; 3321.62; 469.63	−74.66 (−213.70…64.38)

MD is the mean difference, PCOS minus control. Wang publishes mean ± SEM in kg: 3.37 ± 0.09 and 3.56 ± 0.07; SEMs of 90 and 70 g were converted to SDs. Xie reports SDs. MD variances were 13 000.00 and 5032.67 g². Individual CIs were calculated using a normal approximation and are not presented as published; inverse-variance weights were 27.91 and 72.09%.

The restricted maximum likelihood estimate of between-study variance reached the zero boundary. With modified Knapp–Hartung inference and one degree of freedom, the pooled interval was much wider than the individual study intervals (Table 10). The normal-approximation sensitivity interval also crossed zero. Neither analysis established a difference or equivalence between groups.

Table 10. Pooled estimate and heterogeneity

Method	Mean difference, g	Heterogeneity
Random effects; REML; modified Knapp–Hartung, $q^* = \max(1,q)$, df = 1	−106.85 (95% CI −872.19 to 658.49)	Q = 0.738; df = 1; P = 0.390; I^2 = 0%; τ^2 = 0 g²
Normal-approximation sensitivity analysis	−106.85 (95% CI −224.91 to 11.21)	At τ^2 = 0, this coincides with the common-effect estimate. This method also does not confirm a difference.

REML, restricted maximum likelihood. A zero heterogeneity estimate with two studies was not evidence of biological homogeneity. These intervals described sampling uncertainty and did not quantitatively correct confounding or selection bias.

Robustness checks did not support a strong causal interpretation (Table 11). Leaving either report out retained a negative point estimate but yielded only a single, imprecise contrast. Excluding both unadjusted cohorts because of unresolved confounding left no quantitative pool. Consequently, the exploratory result was not described as robust to bias exclusion.

Table 11. Checks of heterogeneity and robustness

Check	Finding	Consequence
Heterogeneity	I^2 = 0%, τ^2 = 0, Q P = 0.390, k = 2.	Too little information for reliable between-study variance estimation; zero did not prove homogeneity.
Exclusion of Wang 2020	Xie remained: MD −74.66 g (calculated CI −213.70 to 64.38).	Direction remained negative but compatible with no difference; not a repeat meta-analysis.
Exclusion of Xie 2024	Wang remained: MD −190.00 g (calculated CI −413.47 to 33.47).	Interval crossed zero; I^2 and τ^2 were not evaluated for one study.
Exclusion of studies at very high risk	Separate ROBINS-E forms for the two included raw weight contrasts have not been completed. They cannot be declared low risk on the basis of objective weighing.	The earlier very high risk related to NGF/ceRNA, not automatically to all outcomes in the papers. A conservative analysis excluding both studies because of uncontrolled confounding leaves no pool. The result cannot be called robust to exclusion of bias.
Change interval method	Modified Knapp–Hartung and normal intervals had the same point estimate but very different precision.	Neither established a nonzero difference; absence of significance was not absence of a clinically relevant association.
Within-report sensitivity	Berns depended on reference fertility/conception. Several Wu S lipid associations attenuated with adjustment; one	These were published within-dataset checks, not independent replications or a new individual-participant reanalysis.

	PE and one PC contrast persisted.	
Prediction and modifiers	No prediction interval, meta-regression or subgroup meta-analysis at k = 2.	Insufficient information for a new-population prediction or credible moderator assessment.

Bias certainty and selective reporting

Across the ten assessed exposure contrasts, two had some concerns, six had high risk and two unadjusted molecular contrasts had very high concern at screening. These labels applied to the specified result, not to every outcome in a paper. The cross-sectional lipid comparison was kept outside the ROBINS-E total. Table 12 summarizes the result-level judgments and the principal reasons.

Table 12. Risk of bias for individual findings

Report and target	Judgment	Principal concern
Polinski 2023; cg02372539 with hirsutism	Some concerns	Self-reported phenotype, selection into specimen analysis and residual familial confounding despite broad adjustment.
Berns 2025; volume at 11 weeks	Some concerns	Selection, fertility-related reference groups and interpretation of the adjusted target.
Lambertini 2017; methylation discoveries	High	6 + 6; incomplete control of clinical differences and cell composition.
Ge 2025; metabolomic contrast	High	Clinical confounding and selection of uncomplicated pregnancies.
Ge 2026; adjusted omics contrast	High	Selection and adjustment for variables potentially downstream of PCOS.
Wu S 2026; amniotic omics contrast	High	Treatment/plurality imbalance, small subsets and analytical selection.
Talmo 2024; adjusted birth-size contrast	High	Trial-derived cases versus an external population; cohort selection and residual confounding.
Chen 2021; childhood obesity	High	Combined exposure, maternal diagnosis timing and incomplete adiposity control.
Xie 2024; unadjusted ceRNA contrast	Very high at screening	No adequate confounding control for a causal molecular interpretation.
Wang 2020; unadjusted human NGF contrast	Very high at screening	Clinical confounding not adequately addressed in the selected causal comparison.
Wu X 2026; child lipid comparison	JBI appraisal; important limitations	Matched cross-sectional sample with residual confounding and selected follow-up; no ROBINS-E category assigned.

These are structured result-level appraisal judgments. Official ROBINS-E signaling forms were not completed in full for every result. The two screening-level judgments were not seven-domain completed assessments. No numerical quality score was calculated.

Outcome-specific certainty was low or very low in the assessed contrasts (Table 13). No overall GRADE label was assigned to placental omics as a class because it contained no single common outcome. Certainty of a biomarker–disease pathway was not graded when the relevant longitudinal mediation evidence was absent from the extracted set. A large register sample and small P values were not used as reasons to upgrade causal certainty.

Table 13. Certainty of evidence by outcome

Outcome	GRADE	Reasons and scope
Obesity at 10–16 years	Very low	One register cohort; serious bias and indirectness for pure PCOS because exposure included anovulatory infertility. CI precision alone did not resolve these limitations.
Adjusted birth-weight z score	Very low	One external cohort comparison; serious selection/confounding concerns. Applies to anthropometry, not later disease.
Total/LDL cholesterol at 4–6 years	Very low	Selected girls after ART, residual confounding, no compatible adjusted-effect CI or significance threshold.
Placental volume at 11 weeks versus subfertile controls	Low	One cohort; no upgrading. Direct for the specified ultrasound comparison, not a child disease endpoint.
Neonatal cg02372539 with maternal hirsutism	Low	One adjusted cohort; no independent locus-specific replication or established clinical meaning.
Human NGF and amniotic PC/PE contrasts	Very low	Important confounding/selection concerns; molecular changes were not validated clinical surrogates.
Exploratory raw birth-weight pool	Very low	Two unadjusted, selected cohorts and extremely wide conservative CI; no established causal independence from

		maternal factors.
Omics overall or molecular marker → disease	Not assigned	No coherent common endpoint for omics overall; no extracted longitudinal mediation evidence for the complete causal chain.

Profiles are provisional for the current evidence set. Observational evidence started at low certainty; reductions reflected specific bias, indirectness or imprecision. Inconsistency was not automatically downgraded for one study, and publication bias was not declared absent because no formal test was possible.

No outcome had ten independent comparable studies. Neither funnel plots nor Egger testing was performed. The absence of a test could not exclude publication bias, while potential small-study effects would not by themselves prove selective publication. Omics analyses additionally allowed multiple choices of targets, thresholds, normalization procedures and models. False-discovery-rate correction addressed one aspect of multiplicity but did not establish preregistration or eliminate selection of reported analyses.

DISCUSSION

The evidence supported a heterogeneous association pattern rather than a uniform offspring phenotype. Lower adjusted birth-size scores, a register association with later obesity and a lipid difference in selected young girls could coexist without representing one continuous disease trajectory. Different ages, maternal phenotypes and sampling frames could contribute to this pattern, but the current studies did not establish these characteristics as effect modifiers. A nonsignificant growth contrast in one cohort and a significant obesity association in another cannot be interpreted as a proven transition from normal early growth to later obesity.

The distinction between an association with PCOS and an effect attributable to PCOS is central. Maternal adiposity may precede diagnosis, share causes with the syndrome or lie within a longer developmental process that the available cohorts cannot separate. Gestational diabetes and fertility treatment can follow diagnosis and influence both the probability of entering a study and the child outcome. Including all these variables in one model is therefore not a universal solution. A total-effect question, a direct-effect question conditional on selected pregnancy factors and a descriptive comparison among assisted conceptions are different estimands. They should not be pooled solely because each coefficient is labeled adjusted.

In Talmo et al. (2024), adjustment for BMI changed the standardized weight contrast, but this change cannot be explained by a single mechanism. In Chen et al. (2021), the relatively precise association with obesity is limited by the combined exposure and the timing of diagnosis; in Berns et al. (2025), the fertility status of the reference group is important.

Placental and epigenetic hypotheses

The placenta is a plausible site of maternal–fetal interaction, but the findings did not validate a shared disease mechanism. Ultrasound volume, placental weight, neurotrophin expression, RNA networks and metabolite concentrations measured different processes at different stages of pregnancy. Combining them into a generic placental dysfunction outcome would remove the very distinctions needed to explain their relation to offspring health. Their convergence was better expressed as a set of testable hypotheses about vascular development, immune regulation and substrate handling.

For methylation, the strongest interpretive boundary was locus and tissue specificity. The phenotype-specific neonatal result in Polinski et al. (2023) did not imply that all maternal PCOS phenotypes have a common methylation signature. The cord-blood pilot findings did not replicate the neonatal loci merely because some annotated genes belonged to related pathways. Differences in cell mixtures, assay coverage and multiple-testing procedures could generate different discovery patterns even under similar biology. Conversely, failing to find a shared significant locus in small studies did not establish absence of epigenetic effects.

A defensible mechanistic chain would require more than concurrent molecular and birth-weight measurements. A candidate placental signal would need reliable measurement, evidence of temporal precedence, an association with later child outcomes, appropriate control of shared causes and replication in an independent population. Functional perturbation could then test a specific link, provided that the experiment reproduced a relevant exposure range and tissue context. The current cell and animal findings addressed narrower regulatory questions and could not fill the missing longitudinal human links.

Interpretation of the exploratory meta-analysis

The birth-weight calculation was useful mainly because it made uncertainty explicit. Restriction to singleton girls delivered by cesarean improved compatibility but created a narrow target population. Nonoverlapping recruitment years reduced concern about direct overlap between the two reports, yet both came from one center and used unadjusted means. The pooled estimate therefore described these selected samples rather than an average causal effect across all pregnancies with PCOS.

The zero estimate of τ^2 should not be read as reassurance. With only two studies, a heterogeneity estimator has little information, while the conservative t-based interval has one degree of freedom. Its width reflected the fragility of small-k inference, not an additional biological finding. The normal interval supplied a sensitivity comparison but could not overcome confounding or selection. Neither interval justified a clinical claim of reduced birth weight, and neither established equivalence. This is consistent with methodological cautions about evidence synthesis from very few studies (Bender et al., 2018).

CONCLUSIONS

Maternal PCOS was associated with selected offspring clinical measures and with heterogeneous placental and epigenetic findings, but the evidence did not isolate a general causal effect from adiposity, gestational diabetes, infertility treatment

and other shared determinants. The conclusions for each evidence stream are retained separately in Table 14. Molecular findings support hypotheses for validation rather than a demonstrated pathway to childhood disease. The exploratory birth-weight estimate was too imprecise and confounded for clinical causal inference.

Table 14. Conclusions by stream

Stream	Conclusion
Clinical outcomes	Individual studies identified associations with obesity and lipid profiles. Independence of these associations from maternal obesity, GDM, infertility, and its treatment has not been established across the entire set. Comparable adjusted effects were not pooled. The exploratory birth-weight estimate is imprecise and does not support a causal conclusion.
Placental findings	Differences in vascular development, expression and metabolism were observed without a common validated marker. Ultrasound measures, placental mass and omics targets retained separate interpretations.
Epigenetic findings	Signals depended on phenotype and tissue. Independent quantitative replication of the same locus under compatible conditions was not established in the extracted evidence.
Animals and cells	Experiments supported selected regulatory hypotheses. Null findings across ages/generations were retained; human disease risk was not inferred from these models.
Certainty	The earlier GRADE assessments remain provisional. Certainty for the exploratory birth-weight pool is very low because of uncontrolled confounding and extremely wide uncertainty; there is no direct evidence for the complete marker → disease causal pathway.

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Author contributions: proposed allocation for confirmation by all authors before submission.
E.S. Bychkova — review conception and design, formulation of the research question, drafting and integration of manuscript sections.
S.A. Bagova — development of the search strategy and eligibility criteria, organization of bibliographic records and search documentation.
R.E. Khachaturova — extraction of study characteristics, description of PCOS diagnostic criteria, tissues, and molecular methods.
S.M.-B. Tumgoeva — analysis of placental and epigenetic findings, comparison of molecular findings and experimental data.
B.M. Agirova — analysis of clinical and metabolic outcomes, assessment of the roles of maternal obesity, gestational diabetes, and infertility treatment.
A.T. Abdurakhmanova — risk-of-bias assessment methodology, preparation of outcome-specific certainty-of-evidence profiles.
D.M. Tosunova — statistical methodology, verification of effect estimates and confidence interval calculations, heterogeneity and sensitivity analyses.
Ch.N. Gadimova — verification of bibliographic information and citations, preparation of tables and the reference list, scientific editing of the manuscript.
Ethics: This review analyzed published aggregate data and involved no new recruitment or access to identifiable participant data.
Data availability: Numerical inputs and reconstructed effect estimates are provided in Tables 9–11; source publications are identified in the references. No individual participant dataset was analyzed.

Calculation appendix
Reproducible calculations based on published aggregate data are presented below; they are not an analysis of individual observations or a repeat multivariable regression. All new CIs are identified as calculated; additional nominal methylation intervals do not replace the FDR assessment in the original source.

Conversion of source measures and individual effects
For Wang, nPCOS = 20 and ncontrol = 32. Means of 3.37 and 3.56 kg are converted to 3370 and 3560 g. Published SEMs of 0.09 and 0.07 kg correspond to 90 and 70 g. SDPCOS = $90 \times \sqrt{20} = 402.492$ g; SDcontrol = $70 \times \sqrt{32} = 395.980$ g. Using SEM instead of SD would incorrectly underestimate the variance and overestimate precision.
$MD_1 = 3370 - 3560 = -190.000$ g. $v_1 = (90^2 \times 20)/20 + (70^2 \times 32)/32 = 8100 + 4900 = 13\,000.000$ g²; $SE_1 = \sqrt{13\,000} = 114.018$ g. Calculated 95% CI = $-190 \pm 1.959964 \times 114.018 = -413.470 \ldots 33.470$ g.
For Xie, SDs were published, so no additional conversion is needed. $MD_2 = 3246.96 - 3321.62 = -74.660$ g. $v_2 = 592.73^2/103 + 469.63^2/136 = 3410.960 + 1621.708 = 5032.668$ g². $SE_2 = 70.941$ g; calculated 95% CI = $-74.66 \pm 1.959964 \times 70.941 = -213.702 \ldots 64.382$ g.

Pooled estimate and between-study variation
At $\tau^2 = 0$, weights $w_i = 1/(v_i + \tau^2)$ are 0.000076923 and 0.000198702 g^{-2}; the sum of weights is 0.000275625 g^{-2}. Normalized weights $w_i/\Sigma w_i$ are 0.279086 and 0.720914. $\mu = \Sigma(w_i \times MD_i)/\Sigma w_i = 0.279086 \times (-190) + 0.720914 \times (-74.66) = -106.850$ g. $SE\mu = \sqrt{(1/\Sigma w_i)} = 60.234$ g.

REML was obtained by minimizing the restricted negative log-likelihood $L(\tau^2) = \frac{1}{2}[\Sigma \ln(v_i + \tau^2) + \ln \Sigma w_i + \Sigma w_i(MD_i - \mu)^2]$, with the boundary $\tau^2 = 0$ checked. The additive constant independent of τ^2 is omitted; for these data, the minimum is at the boundary, $\tau^2 = 0$ g². This is a model estimate, not proof of the absence of true variation.
$Q = \Sigma w_i(MD_i - \mu)^2 = 0.531843 + 0.205891 = 0.737734$. Degrees of freedom $k - 1 = 1$; $P = P(\chi^2_1 \geq Q) = 0.390388$. $I^2 = \max[0, (Q - 1)/Q] \times 100\% = 0\%$. At $k = 2$, the sensitivity of heterogeneity assessment is extremely limited.
For modified Knapp–Hartung, $q = Q/(k - 1) = 0.737734$; $q^* = \max(1, q) = 1$. $SEmKH = \sqrt{(q^*/\Sigma w_i)} = 60.234$ g. The critical $t_{0.975;1} = 12.706205$. 95% CI = $-106.850 \pm 12.706205 \times 60.234 = -872.194 \ldots 658.494$ g. The wide interval is associated with one degree of freedom.
For the normal sensitivity analysis, 95% CI = $-106.850 \pm 1.959964 \times 60.234 = -224.906 \ldots 11.206$ g. Neither the conventional nor the conservative interval supports a nonzero difference; their different widths do not justify selecting a more convenient method on the basis of statistical significance. Intermediate quantities are summarized in Table 15.

Table 15. Intermediate quantities and verification of the final calculation

Quantity	Wang 2020	Xie 2024
PCOS / control sample size	20 / 32	103 / 136
SDPCOS / SDcontrol, g	402.49 / 395.98	592.73 / 469.63
MD, g	−190.00	−74.66
Variance, g²	13000.00	5032.67
SE, g	114.018	70.941
Absolute weight, g^{-2}	0.000076923	0.000198702
Normalized weight, %	27.91	72.09
Contribution to Q	0.531843	0.205891

After excluding Wang, Xie's MD of −74.66 g remains, with a CI of −213.70…64.38 g; after excluding Xie, Wang's MD of −190.00 g remains, with a CI of −413.47…33.47 g. In each case $k = 1$, so a repeat meta-analysis, I^2, and τ^2 are not calculated. Consistency in direction does not imply robustness to confounding.

Additional intervals for methylation loci

For three CpGs from Polinski et al. (2023), nominal Wald intervals $\beta \pm 1.959964 \times SE$ were calculated from the published coefficients and standard errors; they refer to individual coefficients comparing PCOS with hirsutism against no PCOS. The intervals are not adjusted for multiple testing. The published β and SE values are rounded, so the calculation is also approximate; the results are presented in Table 16.

Table 16. Calculated nominal intervals for methylation coefficients

CpG	β; SE	Calculated 95% CI	Source FDR P
cg02372539	−0.0807; 0.010	−0.1003…−0.0611	0.0095
cg08471713	0.0773; 0.014	0.0499…0.1047	0.0164
cg17897916	0.0501; 0.009	0.0325…0.0677	0.0095

Example for cg02372539: $-0.0807 \pm 1.959964 \times 0.010 = -0.1003 \ldots -0.0611$. β on the methylation proportion scale corresponds to a difference of −8.07 percentage points; the interval is −10.03…−6.11 percentage points. This is not a relative reduction of 8.07% or a disease risk. Similarly, the difference is +7.73 percentage points for cg08471713 and +5.01 percentage points for cg17897916. No overall epigenetic effect was calculated from these three loci.
The formulas for converting continuous effects are consistent with the Cochrane Handbook, Chapter 6 (Higgins et al., 2024, Chapter 6). Sensitivity analysis does not change the causal limitations; the available summary data cannot be used to calculate new individual-level adjustments for BMI, GDM, or ART, establish mediation, or reconstruct unavailable clinical outcomes.

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