

From fetal life to adulthood: cardiometabolic health of offspring conceived by assisted reproductive technologies, a systematic review

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Importance: The number of children conceived through assisted reproductive technologies (ART) continues to increase worldwide, raising questions regarding their long-term cardiometabolic health. Both ART procedures and parental infertility may contribute to the developmental programming of cardiometabolic outcomes.

Objective: To systematically evaluate cardiometabolic health in ART-conceived offspring across developmental stages, assess the impact of specific ART procedures, and examine the contribution of parental infertility.

Evidence Review: Following Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines and International Prospective Register of Systematic Reviews registration (CRD420251145460), PubMed and Embase were searched through April 30, 2026, for studies evaluating cardiometabolic outcomes in ART-conceived offspring. Because of substantial heterogeneity, findings were synthesized narratively according to developmental stage, ART modality, and outcome category.

Findings: Fifty-five studies met the inclusion criteria. From fetal life through adolescence, ART-conceived offspring frequently exhibited subtle cardiovascular differences, including mild cardiac remodeling, modest elevations in blood pressure, and early endothelial dysfunction. Metabolic findings, including insulin resistance and adiposity, were less consistent. Although several cohorts reported higher blood pressure values and vascular alterations in ART offspring, these differences were generally modest and remained within normal physiological ranges. A large multicohort analysis found no overall differences in blood pressure, heart rate, triglycerides, or insulin resistance traits, although higher childhood low-density lipoprotein cholesterol concentrations and adiposity attenuated with age. By adulthood, most cardiometabolic parameters appeared comparable between ART-conceived offspring and offspring conceived without ART. No consistent adverse long-term effects were identified for intracytoplasmic sperm injection, frozen embryo transfer, or preimplantation genetic testing. Similar cardiometabolic profiles were reported in offspring of subfertile parents conceived without ART and in ART-conceived offspring, supporting an independent contribution of parental infertility.

Conclusions and Relevance: This review found no evidence of a major adverse cardiometabolic effect of ART in offspring. However, subtle cardiovascular differences have been reported from fetal life through adolescence, whereas metabolic findings remain less consistent. These alterations are generally mild, age-dependent, and often remain within normal physiological ranges, although their long-term clinical significance remains uncertain. Future studies should include offspring of subfertile parents conceived without ART and extend follow-up into adulthood to clarify whether early-life differences represent transient developmental adaptations or markers of increased cardiovascular susceptibility later in life. (Fertil Steril® 2026;126:615–32. ©2026 by American Society for Reproductive Medicine.)

Key Words: Assisted reproductive technology, cardiometabolic health, blood pressure, offspring, parental infertility

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Since the birth of Louise Brown in 1978, assisted reproductive technologies (ART) have enabled millions of infertile couples to conceive. More than 10 million children have been born worldwide through these techniques since 1978 (1). Assisted reproductive technology encompasses a range of procedures, including in vitro fertilization (IVF), intracytoplasmic sperm injection (ICSI), frozen embryo transfer (FET), and preimplantation genetic testing (PGT). Although ART has revolutionized reproductive medicine, concerns have emerged regarding the long-term health of offspring conceived through these methods.

The Developmental Origins of Health and Disease hypothesis posits that environmental exposures during critical developmental windows can program long-term health outcomes (2). The ART procedures occur during periods of extensive epigenetic reprogramming in the gametes and early embryo, raising the possibility that they could influence developmental trajectories and subsequent cardiometabolic health (3). Animal studies have demonstrated that culture media composition, ovarian hyperstimulation, and embryo manipulation can alter offspring cardiovascular and metabolic phenotypes (4, 5). In humans, several studies have reported associations between ART and altered blood pressure, vascular function, and metabolic parameters in offspring, although findings have been inconsistent (6).

Importantly, the interpretation of these associations is complicated by the potential confounding role of parental infertility itself. Infertile couples differ from fertile couples in ways that may independently affect offspring health, including older parental age, higher prevalence of metabolic syndrome, and genetic or epigenetic factors related to subfertility (7, 8). Disentangling the effects of ART procedures from those of underlying parental infertility remains a major challenge in this field.

The primary objective of this systematic review is to synthesize the current evidence on cardiometabolic health outcomes in ART-conceived offspring compared with offspring conceived without ART. Secondary objectives include: evaluating whether specific ART modalities (IVF, ICSI, FET, and PGT) are differentially associated with cardiometabolic outcomes; assessing whether observed associations vary by offspring age (fetal, childhood, adolescence, and adulthood); and examining the contribution of parental infertility to observed differences by reviewing studies. Results are reported according to the age of the children and the specific ART procedure used, with particular attention to the role of parental infertility as a potential confounder.

MATERIALS AND METHODS

Protocol and registration

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 guidelines (9) and was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO; registration number CRD420251145460).

Search strategy

A comprehensive literature search was performed in PubMed and Embase up to 20 March 2025, corresponding to the International Prospective Register of Systematic Reviews (PROSPERO) registration date. To ensure inclusion of the most recent evidence, the literature search was updated on 30 April 2026 before manuscript submission, and any newly relevant studies were incorporated into the review. The search strategy combined Medical Subject Headings terms and free-text keywords related to: assisted reproductive technology (ART, IVF, ICSI, FET, and PGT); cardiovascular outcomes (blood pressure, vascular function, and cardiac structure and function); metabolic outcomes (glucose metabolism, insulin resistance, lipid profile, and adiposity); and parental infertility. Relevant articles were in addition manually screened to identify additional eligible studies (backward citation tracking).

Eligibility criteria

Studies were included if they met the following criteria: human studies; cohort, case-control, or cross-sectional design; assessment of cardiovascular or metabolic outcomes in ART-conceived offspring; comparison with conception without ART offspring or population norms; published in English. Studies were excluded if they: focused solely on perinatal outcomes (birth weight and gestational age) without cardiometabolic follow-up; were case reports; and lacked a comparison group.

Study selection

Two reviewers (MS and PF) independently screened titles and abstracts, followed by a full-text review of potentially eligible articles. Disagreements were resolved through discussion and consensus.

Data extraction

Data were extracted independently by two reviewers (MS and PF) using a standardized data extraction form developed in Microsoft Excel. The form captured: study characteristics (author, year, country, design, and sample size); participant characteristics (offspring age, ART modality, and parental infertility status); outcome measures (cardiovascular and metabolic parameters); and results (effect sizes, confidence intervals, *P* values). Discrepancies were resolved by consensus.

Risk of bias assessment

Study quality was assessed independently by two reviewers using the Newcastle-Ottawa Scale (NOS) for cohort and case-control studies (10). The NOS evaluates three domains: selection of study groups, comparability of groups, and ascertainment of outcome. We acknowledge that the NOS has recognized limitations, including subjective scoring criteria and limited assessment of confounding (11). Studies were classified as Good (8–9 points), Fair (6–7 points), and Poor (≤ 5 points). Publication bias was assessed qualitatively

by examining study characteristics. Formal funnel plot analysis was not performed because of the narrative synthesis approach and heterogeneity in outcome measures across studies.

Data synthesis

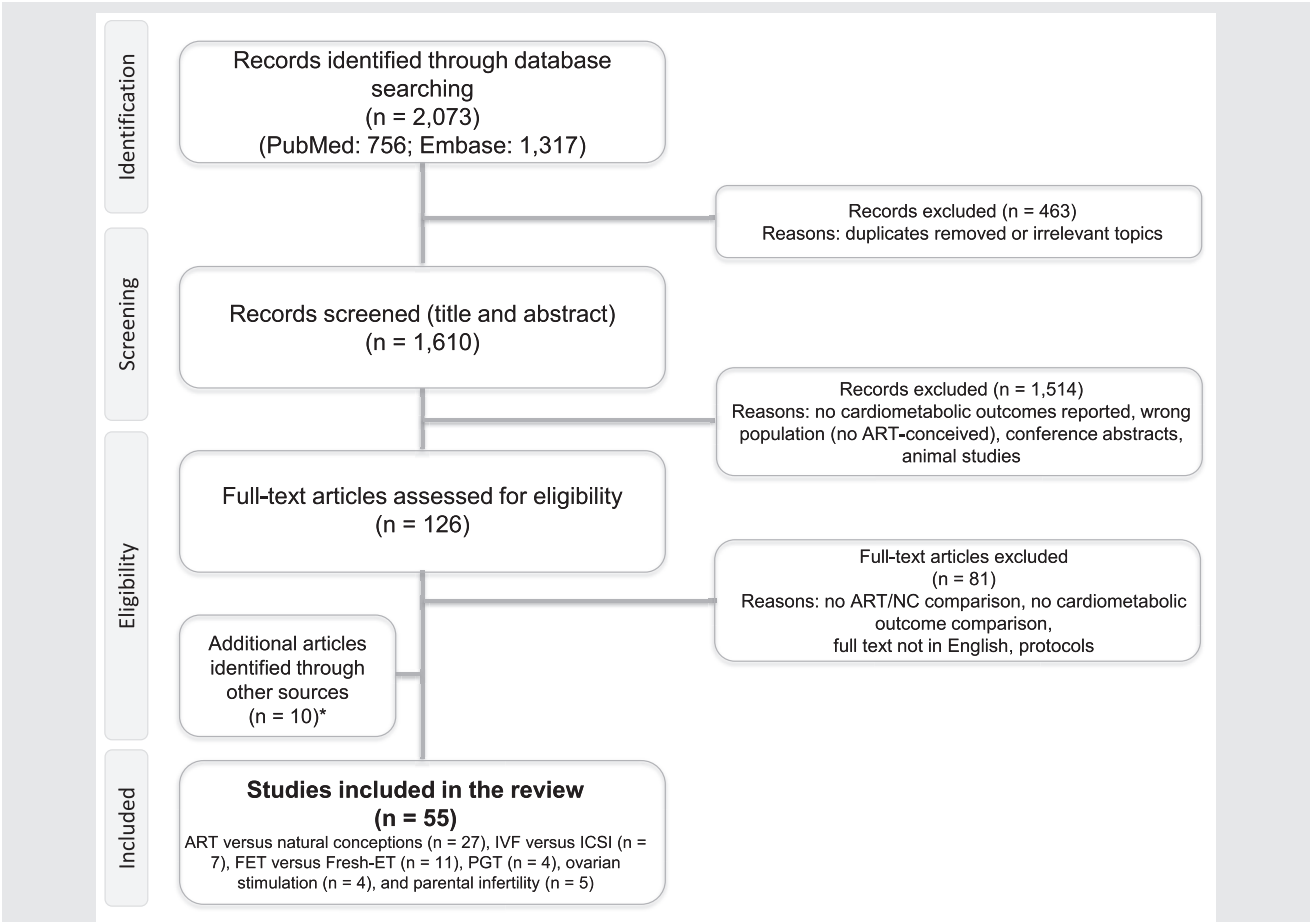
Because of substantial heterogeneity in study designs, ART modalities, offspring ages, outcome definitions, and measurement methods, meta-analysis was not feasible. Results were synthesized narratively, organized by: offspring age group (fetal, childhood, adolescence, adulthood); ART modality (IVF, ICSI, FET, and PGT); and outcome category (cardiovascular and metabolic). Where multiple studies reported the same outcome in comparable populations, findings were qualitatively summarized. We did not apply a formal grading of recommendations, assessment, development, and evaluations assessment because of the narrative synthesis approach

and the observational nature of all included studies, which inherently limits the certainty of evidence.

RESULTS
Study selection

The systematic literature search identified 2,073 records: 756 from PubMed and 1,317 from Embase. After removal of 463 records (duplicates or irrelevant topics), 1,610 records were screened on title and abstract, of which 126 articles were retrieved for full-text assessment. Of these, 81 were excluded for the following reasons: perinatal outcomes only, no cardiometabolic outcome comparison, no ART or conception without ART comparison group, and non-English language. An additional 10 studies were identified through citation screening and other sources. A total of 55 studies met the inclusion criteria for this systematic review (Fig. 1).

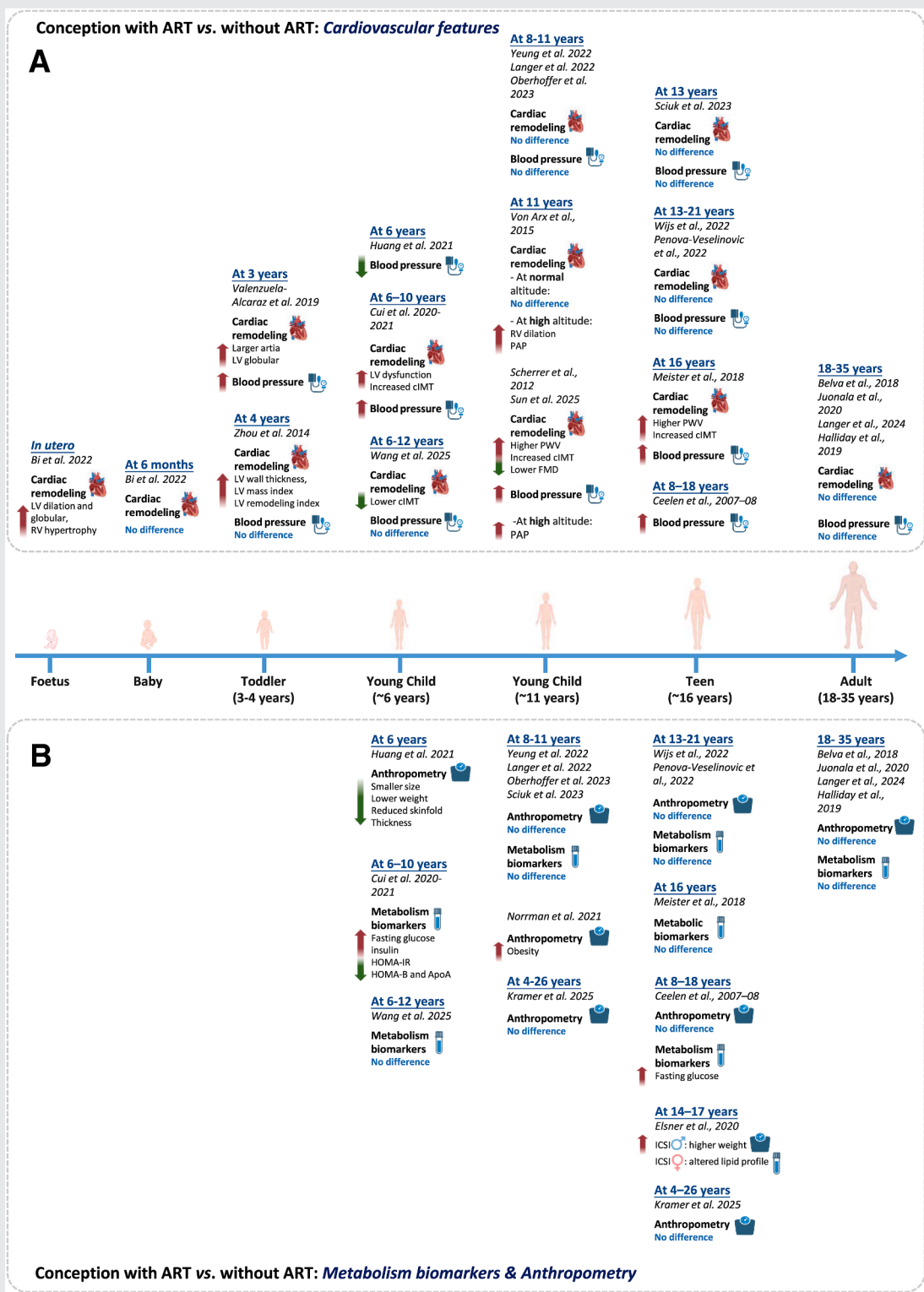
FIGURE 1



Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of study selection. A total of 2,073 records were identified through database searching (PubMed and Embase). A total of 55 studies were included in the narrative synthesis, distributed across six thematic categories: overall ART vs. conception without ART, fertilization method: IVF vs. ICSI, embryo transfer modality: frozen embryo transfer (FET) vs. fresh-ET, preimplantation genetic testing (PGT), ovarian stimulation, and parental infertility.* Of the 10 additional studies, eight were identified through citation searching and two were incorporated during peer review.

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FIGURE 2



Developmental timeline of cardiometabolic outcomes in ART-conceived offspring vs. offspring conceived without the assistance of ART. Overview of (A) cardiovascular and (B) metabolic/anthropometric effects, except Elhakeem's study (multiple time points: no difference in blood pressure between groups; higher cholesterol in ART offspring attenuating with age). ApoA = apolipoprotein A; ART = assisted reproductive technology; cIMT = carotid intima-media thickness; FMD = flow-mediated dilation; HOMA-B = homeostasis model assessment of beta-cell function; HOMA-IR = homeostatic model assessment of insulin resistance; ICSI = intracytoplasmic sperm injection; LV = left ventricle; PAP = pulmonary arterial pressure; PWV = pulse wave velocity; RV = right ventricle.

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The included studies encompassed diverse study designs (prospective cohorts, retrospective population-based cohorts, cross-sectional studies) and follow-up periods ranging from fetal life to young adulthood. They assessed cardiovascular and metabolic outcomes in offspring conceived through ART compared with offspring conceived without ART, and examined the specific contributions of individual ART procedures (fertilization method, embryo transfer modality, PGT, ovarian stimulation) and parental infertility. Results are presented according to six thematic subsections, with findings organized chronologically across four developmental periods: fetal period, neonatal period, and early childhood; childhood; adolescence; and young adulthood and adulthood.

Study quality assessment

Study quality was assessed using the Newcastle–Ottawa Scale (NOS). Across all 55 included studies (58 NOS assessments, because 3 studies contributed entries to multiple sections), the overall methodological quality was high (45 assessments rated Good [78%] and 13 rated Fair [22%]; no study rated Poor—[Supplemental Table 1](#), available online). By thematic section, the quality assessments were as follows: conception with the assistance of ART vs. without ART (n = 27 studies): 25 Good and 2 Fair; IVF vs. ICSI (n = 7 studies): 4 Good and 3 Fair; FET vs. fresh-ET (n = 11 studies): 8 Good and 3 Fair; PGT (n = 4 studies): 2 Good and 2 Fair; hormonal stimulation (n = 4 studies): 3 Good and 1 Fair; parental infertility (n = 5 studies): 2 Good and 3 Fair.

Conception with ART vs. without the assistance of ART

For this question, a total of 27 studies were analyzed, detailed in the [Supplemental Table 2](#), and synthesized in [Figure 2](#) (12–38).

Fetal period, neonatal period, and early childhood. Multiple studies documented cardiac structural and functional differences in ART-conceived fetuses and young children. A systematic review by Tasiias et al. (39) confirmed that ART fetuses exhibit cardiac remodeling and altered cardiac function detectable by echocardiography in utero. Bi et al. (27) performed fetal echocardiography between 28 and 32 weeks of gestation in 88 ART-conceived fetuses and 85 fetuses conceived without ART. The ART-conceived fetuses exhibited a larger and more globular left ventricle (LV), reduced LV systolic deformation, and a larger right ventricle than fetuses conceived without ART. Importantly, postnatal follow-up at 0–2 months and 6 months after birth showed no significant differences, suggesting early normalization of these cardiac changes (27).

Valenzuela-Alcaraz et al. (20) followed 80 ART pregnancies and 80 pregnancies conceived without ART from fetal life to the age of 3 years. At age 3, ART children demonstrated persistent cardiac remodeling with larger atria and more globular ventricles, signs of systolic and diastolic dysfunction, elevated blood pressure, and thicker carotid walls (20).

Similarly, Zhou et al. (15) reported that 4-year-old ART-conceived children (n = 128) had higher LV relative wall thickness, LV mass index, and LV remodeling index than 100 children conceived without ART, after adjustment for age, sex, body surface area, and heart rate.

Childhood. Several studies have assessed cardiometabolic outcomes in school-age ART children, with contrasting results across both cardiovascular and metabolic domains.

Cardiovascular outcomes. Multiple studies have documented elevated blood pressure in school-age ART children. Cui et al. (22) reported significantly higher systolic blood pressure (SBP: 105.5 ± 6.9 vs. 103.5 ± 8.4 mmHg; $P < .001$) and diastolic blood pressure (DBP: 67.2 ± 5.6 vs. 62.2 ± 6.3 mmHg; $P < .001$) in 382 ART-conceived children aged 6–10 years compared with 382 children conceived without ART. In contrast, Huang et al. (25) reported a modest but significant reduction in SBP among 83 ART singleton children compared with 1,095 children conceived without ART (-3 mmHg, 95% confidence interval [CI]: $-6 - 0.5$). Wang et al. (38) found no differences in blood pressure between 51 ART-conceived and 49 children conceived without ART aged 6–12 years, although reporting lower carotid intima-media thickness (cIMT) in the ART group.

Beyond blood pressure, structural and functional cardiac abnormalities have been documented. Indeed, Cui et al. (22) reported echocardiographic evidence of left ventricular systolic and diastolic dysfunction, with an increased risk of ventricular abnormalities, and a significantly increased cIMT in this same cohort (0.54 ± 0.05 vs. 0.41 ± 0.05 mm, $P < .001$).

Metabolic and anthropometric outcomes. Metabolic findings during childhood were similarly heterogeneous across studies. Cui et al. (21), evaluating 380 ART-conceived children and 380 children conceived without ART, reported significantly higher fasting glucose (5.06 ± 0.37 vs. 4.57 ± 0.55 mmol/L, $P < .001$), fasting insulin (48.4 ± 23.6 vs. 37.0 ± 24.3 pmol/L, $P < .001$), and homeostatic model assessment of insulin resistance (1.57 [95% CI: $1.01-2.33$] vs. 1.06 [95% CI: $0.69-1.64$], $P < .001$), consistent with a trend toward higher insulin resistance, although all parameters remained within physiological ranges. Pancreatic β -cell function, assessed by homeostasis model assessment of beta-cell function, was significantly lower in ART children (88.7 [95% CI: $64.0-130.6$] vs. 105.1 [95% CI: $69.2-151.1$], $P < .001$). Regarding lipids, serum apolipoprotein A levels were significantly reduced in ART children (1.28 ± 0.19 vs. 1.45 ± 0.26 g/L, $P < .001$), whereas apolipoprotein B levels were not significantly different (21).

However, the landmark multicohort study by Elhakeem et al. (33), encompassing approximately 35,000 ART offspring and 300,000 offspring conceived without ART from 14 European and Australian cohorts followed from birth to 26 years, found no robust long-term differences in blood pressure, heart rate, triglycerides, or insulin resistance traits. This study reported higher total cholesterol and low-density lipoprotein (LDL)-cholesterol in ART offspring during childhood, but these differences attenuated with age. Similarly, higher adiposity was observed in ART children

during childhood, but no significant differences persisted into adulthood (33).

Adolescence. Cardiovascular differences observed in childhood appear to persist into adolescence, although findings remain heterogeneous across studies.

Cardiovascular outcomes. Scherrer et al. (14) provided a detailed vascular analysis in 11-year-old children (65 ART singletons [21 IVF, 44 ICSI] vs. 57 non-ART singletons). The flow-mediated dilation (FMD) was reduced by 25% in ART children ($6.7\% \pm 1.6$ vs. $8.6\% \pm 1.7$; $P < .0001$), although endothelium-independent vasodilation was preserved, suggesting intact vascular smooth muscle function. Pulse wave velocity (PWV), a marker of arterial stiffness, was significantly higher in ART children, as was cIMT. Pulmonary arterial pressure at high altitude (3,450 m) was 30% significantly higher in ART children, indicating increased pulmonary vascular sensitivity to hypoxic stress. In a sibling analysis including five pairs of children (one ART and one non-ART), ART children consistently showed lower FMD, higher pulmonary pressure, faster PWV, and greater cIMT compared with their non-ART siblings (14).

Complementing these findings, Von Arx et al. (16) compared echocardiographic measures in 54 ART-conceived children and 54 children conceived without ART, aged approximately 11 years, under normoxic and hypoxic conditions at high altitude. No differences were detected at low altitude; however, under high-altitude-induced pressure overload and hypoxia, ART children had significantly larger right ventricular end-diastolic area, impaired right ventricular diastolic function, and elevated pulmonary arterial pressure.

Similarly, Sciuk et al. (35) conducted a cohort study on 64 ART-conceived children and 83 children conceived without ART, with a mean age of 13 years. Echocardiographic assessment showed impaired diastolic function, notably with a lower left ventricular ejection fraction ($63.63 \pm 5.17\%$ vs. $65.35 \pm 5.10\%$, $P = .046$). However, differences were no longer significant after adjustment for age, birthweight, and gestational age. No group differences were observed in SBP or DBP, or heart rate, even after statistical adjustment (35).

Meister et al. (18), in a smaller cohort of 54 ART-conceived and 43 adolescents conceived without ART, identified signs of premature vascular aging, including significantly reduced FMD, increased PWV, and greater cIMT. The ART-conceived adolescents also exhibited significantly higher SBP (119.8 ± 9.1 vs. 115.7 ± 7.0 mmHg, $P = .02$) and DBP (71.4 ± 6.1 vs. 69.1 ± 4.2 mmHg, $P = .03$), as well as greater BP variability (18).

In contrast, Langer et al. (28) examined 67 ART-conceived and 86 children conceived without ART (including singletons and twins) at a mean age of 11 years and found no significant differences in cardiac function or arterial stiffness (PWV). Similarly, Oberhoffer et al. (34) evaluated vascular parameters (BP and cIMT), anthropometry, and metabolic biomarkers in 66 ART-conceived and 86 children conceived without ART of comparable age and found no significant differences in vascular or metabolic parameters. Yeung et al.

(32) also reported no increased cardiometabolic risk among children conceived after ART or ovulation induction (OI) compared with children conceived without ART in 8- to 10-year-old children.

Kramer et al. (37) investigated cardiorespiratory fitness and muscle strength in ART offspring from school age to adolescence, finding that ART offspring potentially display increased cardiovascular morbidity, with cardiorespiratory fitness and muscle strength serving as key indicators of cardiovascular outcomes. Two longitudinal studies from the Australian national Growing Up Healthy Study cohort reported largely reassuring results. Wijs et al. (31) performed a multidimensional assessment including anthropometry, BP, arterial stiffness, and health questionnaires in 163 ART and 1,457 non-ART adolescents aged 13–21 years and found no significant differences across most cardiovascular parameters. Similarly, Penova-Veselinovic et al. (30) analyzed the same parameters at three different ages (14, 17, and 20 years) in a cohort of 165 and 1,690 adolescents conceived with and without ART, respectively, and did not observe any deleterious effects of ART on cardiovascular health. In a follow-up study conducted by Ceelen (13) in the Netherlands, cardiovascular outcomes in 225 IVF-conceived children vs. 225 children conceived without ART (aged 8–18 years) were assessed. The IVF children had significantly higher SBP and DBP (109 ± 11 vs. 105 ± 10 mmHg, $P < .001$; and 61 ± 7 vs. 59 ± 7 mmHg, $P < .001$, respectively).

Metabolic and anthropometric outcomes. Metabolic and anthropometric differences in adolescence were reported less consistently. Meister et al. (18) found no differences in metabolic profiles between ART-conceived adolescents and adolescents conceived without ART. Similarly, Penova-Veselinovic et al. (30) reported no deleterious metabolic effects associated with ART in a cohort of 165 ART-conceived and 1,690 adolescents conceived without ART assessed at ages 14, 17, and 20 years.

Ceelen et al. (12) conducted two studies comparing anthropometric and metabolic outcomes in IVF-conceived singletons and singletons conceived without ART aged 8–18 years. In their first study involving 233 IVF-conceived offspring and 233 offspring conceived without ART, anthropometric measurements and dual-energy roentgenogram absorptiometry analyses performed in pubertal children (139 IVF and 143 non-ART) revealed a significantly higher proportion of peripheral fat mass, lower subscapular-to-triceps skinfold ratio, and greater peripheral fat and skinfold thickness in IVF offspring, without differences in overall anthropometric measures or central fat distribution (12). In the second study (including 225 IVF and 225 non-ART children), IVF offspring exhibited slightly but significantly higher fasting glucose concentrations (5.0 ± 0.4 vs. 4.8 ± 0.4 mmol/L, $P < .005$) and peripheral insulin resistance compared with offspring conceived without ART (13). Oberhoffer et al. (34) observed a significantly higher percentage of body fat in ART children (19.30% [15.80%–26.02%] vs. 15.91% [13.21%–21.00%], $P = .007$), despite the absence of differences in other vascular or metabolic biomarkers. Elsner et al. (23) evaluated 272 ART-conceived and 273 adolescents

conceived without ART and reported higher body weight among boys conceived by ICSI (72.6 ± 15.1 vs. 67.7 ± 12.6 kg; $P = .005$) and lower high-density lipoprotein cholesterol (HDL-C) levels among girls conceived by ICSI (HDL-C: 1.5 ± 0.3 vs. 1.6 ± 0.3 mmol/L; $P = .033$). Although parental adjustments attenuated these differences, they remained significant (23). Sciuk et al. (35) found no group differences in weight, height, body mass index (BMI), or body surface area.

Young adulthood and adulthood

Cardiovascular outcomes. In a Belgian cohort study, Belva et al. (17) compared blood pressure measures in 126 young adults conceived by ICSI and 133 peers conceived without ART at 18–20 years of age. No significant differences were observed between groups. Similarly, Juonala et al. (24) investigated cardiovascular health in 172 ART-conceived adults and 78 controls aged 22–35 years using the American Heart Association ideal cardiovascular health score, which incorporates seven metrics (BMI, BP, total cholesterol, fasting glucose, diet, physical activity, and smoking), together with vascular imaging. The investigators found no alterations in cardiovascular risk profile or evidence of atherosclerosis associated with ART conception (24).

Langer et al. (29) evaluated vascular function, BP, and anthropometric parameters in young adults aged 22 years (16 ART, including 9 IVF and 7 ICSI vs. 22 non-ART). Despite the limited sample size, findings were comparable between groups (29).

Halliday et al. (19) followed 193 ART-conceived adults and 86 adults conceived without ART (mean age, 27 years) and found no evidence of increased cardiovascular risk after comprehensive vascular and respiratory assessment.

Similarly, the multicohort study by Elhakeem et al. (33) reported no significant differences in blood pressure or heart rate between ART-conceived and non-ART-conceived young adulthood up to 26 years of age. This large-scale analysis provides the most comprehensive evidence to date, suggesting that many of the cardiovascular differences observed in childhood and adolescence do not translate into clinically significant abnormalities in young adulthood (33).

In contrast, Norrman et al. (26) reported a modest but significant increase in the risk of cardiovascular disease among 122,429 ART-conceived offspring compared with 7,574,685 offspring conceived without ART in a large Nordic registry-based study (mean age 8.6 years, range 0–25 years). However, after adjustments, only the risk of obesity was still significant (aHR 1.14, 95% CI: 1.06–1.23).

Metabolic and anthropometric outcomes. Metabolic and anthropometric differences in young adulthood were reported in some cohorts. In young adulthood, Belva et al. (17) reported lower mean HDL-C concentrations in ICSI-conceived men compared with controls. However, Wijs et al. (31) and Juonala et al. (24) did not observe significant differences across most metabolic or anthropometric parameters. Similarly, the multicohort study by Elhakeem et al. (33) found no significant differences in triglycerides or insulin resistance between ART and non-ART offspring in young adulthood. Finally, Halliday et al. (19) followed 193 ART-conceived and 86 non-ART adults (mean age 27

years) and did not identify increased metabolic risk in the ART group.

Global synthesis – conception with ART vs. without the assistance of ART. Across the developmental trajectory from fetal life to young adulthood, ART-conceived offspring exhibit a pattern of mild cardiovascular remodeling that appears most pronounced from the fetal period through adolescence. Fetal echocardiography studies consistently report larger and more globular ventricles, increased myocardial wall thickness, and subtle functional alterations detectable in utero, with persistence into early childhood despite evidence of partial postnatal normalization in some cohorts. During childhood and adolescence, several studies describe elevated blood pressure, impaired endothelial function, increased arterial stiffness, greater cIMT, and enhanced pulmonary vascular reactivity to hypoxia, supporting the persistence of early vascular alterations, although findings remain heterogeneous. In contrast, metabolic disturbances, including alterations in glucose homeostasis, lipid profiles, and adiposity, are less consistently observed and appear to vary according to population and age. Importantly, the large multicohort study by Elhakeem et al. (33) provides reassuring evidence that many cardiometabolic differences, particularly those related to cholesterol levels and adiposity, attenuate with age, with no robust differences in blood pressure, heart rate, or insulin resistance observed in young adulthood. Nevertheless, registry-based studies continue to suggest a small but significant increase in cardiovascular disease diagnoses among ART-conceived individuals, supporting the need for continued long-term follow-up.

Fertilization method: IVF vs. ICSI

For this question, a total of seven studies were analyzed, detailed in the Supplemental Table 3, and synthesized in the Figure 3 (26, 40–45).

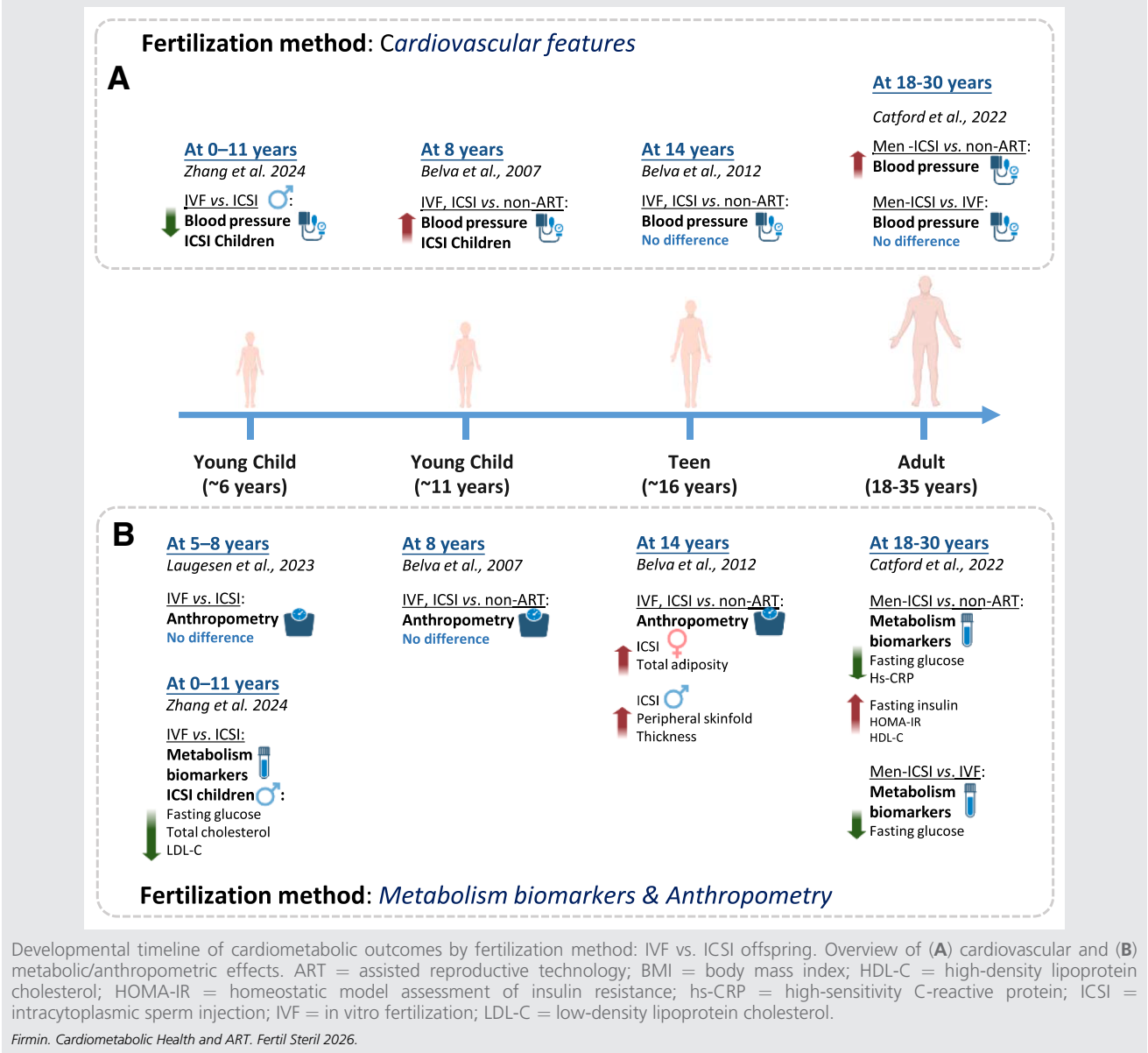
Fetal period, neonatal period, and early childhood. No studies specifically compared fetal or neonatal cardiovascular outcomes between IVF and ICSI offspring during this developmental period.

Childhood

Cardiovascular outcomes. Belva et al. (40) compared 150 ICSI children and 147 children conceived without the assistance of ART at age 8 years and found no differences in weight, height, or head circumference, but significantly higher median DBP (60 [45–75] vs. 55 [35–80], $P < .0001$) and SBP (100 [80–125] vs. 95 [70–120], $P = .0007$) in ICSI children compared with controls. Among the IVF vs. ICSI comparison specifically, Zhang et al. (45) conducted a large prospective cohort study of 4,748 ICSI and 9,448 IVF male singleton offspring aged 0–11 years and found that offspring born to normal-weight fathers via ICSI displayed lower SBP compared with IVF offspring.

Metabolic and anthropometric outcomes. Zhang et al. (45) found that ICSI was associated with lower fasting glucose (z-score adjusted mean difference [MD] -0.13 , 95% CI: -0.23 – -0.03), lower total cholesterol (adjusted MD -0.13 , 95% CI: -0.23 – -0.02), and lower LDL-cholesterol (adjusted

FIGURE 3



MD -0.12 , 95% CI: -0.22 – -0.01) compared with IVF offspring. These associations were modified by paternal BMI: offspring of overweight/obese fathers via ICSI showed lower fasting glucose, total cholesterol, and LDL-cholesterol compared with IVF offspring (45). Laugesen et al. (44) found no association between ICSI vs. conventional IVF and BMI at age 5–8 years in a large Danish cohort of 13,675 ART children.

Adolescence

Cardiovascular outcomes. Belva et al. (41) found no significant differences in resting blood pressure between adolescents conceived by ICSI or without ART at age 14 years, regardless of sex. Similar findings were observed in a smaller

subgroup assessed during stress-induced continuous blood pressure monitoring (41).

Metabolic and anthropometric outcomes. Belva et al. (42) assessed 217 adolescents conceived by ICSI and 223 adolescents conceived without ART at age 14 years. Pubertal girls conceived by ICSI exhibited greater central, peripheral, and total adiposity, whereas pubertal boys conceived by ICSI had a higher sum of peripheral skinfolds than boys conceived without ART (difference 3.5 mm, 95% CI: 0.3–6.6) (42).

Young adulthood and adulthood

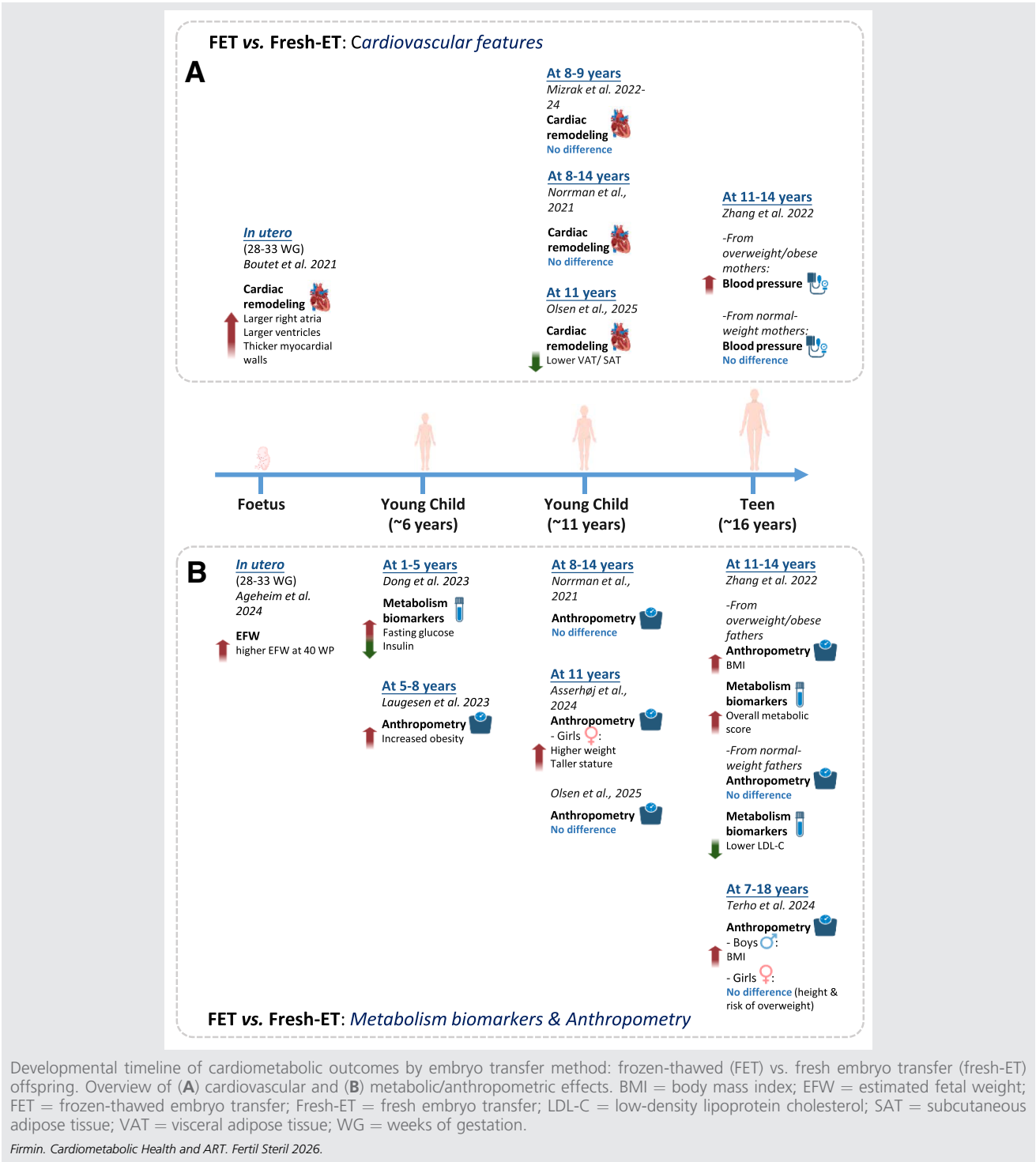
Cardiovascular outcomes. Catford et al. (43) compared 121 men conceived by ICSI (18–24 years), 74 conceived by IVF (25–30 years), and 688 conceived without ART (19–21 years).

Men conceived by ICSI had higher DBP than those conceived without ART (β 4.9, 95% CI: 1.1–8.7) (43). Norrman et al. (26) found that ICSI was not associated with higher cardiovascular disease risk vs. IVF (aHR 1.01, 95% CI: 0.84–1.21) or

obesity (aHR 0.99, 95% CI: 0.90–1.09) in a large Nordic registry-based study.

Metabolic and anthropometric outcomes. Catford et al. (43) further reported that ICSI-conceived men had lower fasting

FIGURE 4



glucose (β -0.7 , 95% CI: -0.9 – -0.5), higher fasting insulin (ratio 2.2, 95% CI: 1.6–3.0), higher homeostatic model assessment of insulin resistance (ratio 1.9, 95% CI: 1.3–2.6), higher HDL-C (β 0.2, 95% CI: 0.07–0.3), and lower high-sensitivity C-reactive protein (ratio 0.4, 95% CI: 0.2–0.6) compared with men conceived without ART. When comparing ICSI-conceived with IVF-conceived men directly, ICSI was associated with lower fasting glucose (β -0.4 , 95% CI: -0.7 – -0.1) (43).

Global synthesis – IVF vs. ICSI. Comparisons between IVF and ICSI offspring reveal a complex and age-dependent cardiometabolic profile. During childhood, ICSI-conceived children exhibit higher blood pressure than offspring conceived without ART, although this difference does not appear to persist into adolescence. In contrast, metabolic differences associated with ICSI show greater consistency across developmental stages, with several studies reporting lower fasting glucose and lipid levels from childhood to young adulthood, particularly in males and in the context of paternal obesity. However, young adult men conceived by ICSI may exhibit higher insulin levels and increased insulin resistance, suggesting compensatory hyperinsulinemia. Anthropometric differences are generally not observed during childhood, although increased adiposity and sex-specific alterations in fat distribution have been described during adolescence, particularly in pubertal girls. Overall, registry-based studies provide reassuring evidence that ICSI is not associated with increased risks of cardiovascular disease or obesity compared with conventional IVF.

Embryo transfer modality: FET vs. fresh embryo transfer

For this question, a total of 11 studies were analyzed, detailed in the [Supplemental Table 4](#), and synthesized in [Figure 4](#) (26, 44, 46–54).

Fetal period, neonatal period, and early childhood

Cardiovascular outcomes. Boutet et al. (46) performed fetal echocardiography at 28–33 weeks of pregnancy in 100 fresh-ET fetuses, 100 FET fetuses, and 100 fetuses conceived without ART. Both fresh-ET and FET fetuses showed signs of cardiac remodeling and suboptimal cardiac function compared with fetuses conceived without ART, with more pronounced changes after fresh-ET than FET (46). Specifically, both groups exhibited larger atria, more globular ventricles, and thicker myocardial walls than fetuses conceived without ART, with reduced tricuspid annular systolic peak velocity and increased left myocardial performance index (46).

Metabolic and anthropometric outcomes. Ageheim et al. (51) conducted a large Swedish registry-based study of 10,970 fresh-ET, 6,520 FET, and 178,518 pregnancies conceived without ART. At 40 weeks, estimated fetal weight was lower after fresh-ET (-1.1% , 95% CI: -1.4 – -0.8) and higher after FET ($+2.1\%$, 95% CI: 1.7–2.6) than in pregnancies conceived without ART (51). Fresh-ET was associated with higher risk of small for gestational age (adjusted odds

ratio [aOR] 1.65, 95% CI: 1.33–2.04) and lower risk of large for gestational age (aOR 0.66, 95% CI: 0.56–0.79) and macrosomia (aOR 0.59, 95% CI: 0.48–0.73) compared with FET (51).

Dong et al. (50) assessed the metabolic profiles in 89 of the 147 children initially recruited, aged 1–5 years, conceived after FET or without ART. Children conceived after FET had lower fasting insulin levels and higher fasting glucose than those conceived after fresh-ET or without ART, suggesting a distinct early metabolic profile in FET offspring (50).

Childhood

Cardiovascular outcomes. Mizrak et al. (47) assessed 50 fresh-ET, 50 FET, and 50 non-ART-conceived children aged 8–9 years using cardiac magnetic resonance imaging and found no differences in cardiovascular function, including arterial stiffness, between fresh-ET and FET groups.

Zhang et al. (49) compared fresh-ET and FET offspring aged 4–11 years born to mothers with overweight/obesity vs. normal weight. In offspring born to mothers with overweight/obesity, FET was associated with higher blood pressure (z-score adjusted MD 0.16, 95% CI: 0.02–0.29) compared with fresh-ET (49).

Metabolic and anthropometric outcomes. Laugesen et al. (44) reported that FET was associated with a 1.5-fold increased risk of obesity at age 5–8 years compared with fresh-ET in a Danish cohort of 13,675 ART children (11,591 fresh-ET, 1,695 FET). Norrman et al. (26) found no association of FET with increased risk of obesity in adjusted analyses in a large Nordic registry-based study.

Asserhøj et al. (52) examined 203 fresh-ET, 200 FET, and 203 non-ART-conceived children aged 7–10 years. No differences in anthropometry or lipid profiles were observed between groups, except that FET-conceived girls had significantly higher weight (standard deviation scores [SDS] 0.35, 95% CI: 0.03–0.67) and height (SDS 0.43, 95% CI: 0.11–0.76) than girls conceived without ART (52).

Olsen et al. (54) assessed 50 fresh-ET, 50 FET, and 50 non-ART-conceived children aged 7–10 years and found a significantly lower visceral-to-subcutaneous adipose tissue (VAT/SAT) ratio in the FET group than in the group of children conceived without ART (mean difference -0.04 , 95% CI: -0.07 – -0.01), suggesting a slightly more favorable fat distribution. No differences in BMI, fat mass, waist-to-hip ratio, or inflammation (high-sensitivity C-reactive protein) were observed (54).

Zhang et al. (49) additionally found that in offspring born to mothers with overweight/obesity, FET was associated with higher BMI (z-score adjusted MD 0.17, 95% CI: 0.04–0.30) and higher metabolic scores (0.54, 95% CI: 0.15–0.94) compared with fresh-ET. In offspring born to mothers with normal weight, FET was associated with lower LDL-cholesterol (-0.12 , 95% CI: -0.22 – -0.02).

Adolescence

Cardiovascular outcomes. Mizrak et al. (48) assessed cardiovascular autonomic nervous function by evaluating heart rate variability in 38 fresh-ET, 34 FET, and 33 non-ART-

conceived children aged 8–12 years. Heart rate variability at rest was lower in both ART groups than in children conceived without ART, but no differences were observed during physiological stress or between fresh-ET and FET offspring (48).

Metabolic and anthropometric outcomes. Terho et al. (53) conducted a large Swedish registry-based study of 2,933 fresh-ET, 1,825 FET, and 31,136 non-ART-conceived singletons aged 7–18 years. The FET boys had higher BMI and increased odds of overweight than fresh-ET boys (aOR 1.14, 95% CI: 1.02–1.27), whereas girls showed similar anthropometric measures across groups, with slightly lower odds of overweight in the FET group than among those conceived without ART (aOR 0.89, 95% CI: 0.80–0.99) (53).

Young adulthood and adulthood. No studies specifically compared cardiometabolic outcomes between fresh-ET and FET offspring in young adulthood or adulthood.

Global synthesis – fresh embryo transfer vs. FET. Fresh-ET and FET offspring exhibit distinct cardiovascular, growth, and metabolic profiles across development. Both modalities are associated with fetal cardiac remodeling and functional alterations compared with fetuses conceived without ART, with more pronounced changes reported after fresh-ET. Growth trajectories also differ, with fresh-ET associated with lower birth weight and increased risk of small for gestational age, whereas FET is consistently associated with higher birth weight and increased risk of large for gestational age. Beyond the fetal period, cardiovascular function appears broadly similar between fresh-ET and FET offspring. In contrast, anthropometric and metabolic findings remain heterogeneous. Several studies report higher BMI and obesity risk in FET offspring, particularly among boys and children of mothers with overweight or obesity, whereas others report no differences or a more favorable fat distribution. Early metabolic differences, including lower fasting insulin levels, have also been described in FET children. Overall, these findings suggest complex interactions between embryo cryopreservation, the endometrial environment, sex-specific factors, and maternal metabolic status in shaping offspring metabolic programming, although their persistence into adulthood remains uncertain.

Preimplantation genetic testing

For this question, a total of four studies were analyzed, detailed in the [Supplemental Table 5 \(55–58\)](#).

Fetal period, neonatal period, and early childhood. No studies specifically assessed cardiovascular or metabolic outcomes in fetuses or neonates conceived after PGT during this developmental period.

Childhood. Zhao et al. (57) conducted a large prospective cohort study comparing 269 ICSI-PGT, 311 ICSI, and 687 IVF singletons aged 1–5 years. No significant differences in physical development, blood pressure, thyroid function, or glucose and lipid metabolism were observed between PGT and non-PGT children in either the overall population or

subgroups, after controlling for confounding factors and correcting for multiple comparisons (57). Similarly, Seggers et al. (58) found no differences in blood pressure or anthropometric measures at age 4 years between children conceived after cleavage-stage PGT (n = 49) and those conceived after ICSI alone (n = 64).

Heijligers et al. (56) assessed 103 ART-PGT children (mainly PGT for monogenic disorders [PGT-M]), 90 ART children, and 58 non-ART-conceived children at age 5 years and found similar growth and health outcomes across groups.

Belva et al. (55) compared 87 children conceived after ICSI-PGT (PGT-M and PGT for structural rearrangements [PGT-SR]) with 87 children conceived after ICSI at age 6 years and found no differences in anthropometric measures or blood pressure.

Adolescence. No studies specifically assessed cardiovascular or metabolic outcomes in adolescents conceived after PGT.

Young adulthood and adulthood. No studies specifically assessed cardiovascular or metabolic outcomes in young adults or adults conceived after PGT.

Global synthesis – PGT. Available childhood data suggest that PGT is not associated with adverse cardiometabolic outcomes, with similar growth, blood pressure, and metabolic profiles observed across PGT, ART, and non-ART groups. Long-term follow-up into adolescence and adulthood is still required.

Ovarian stimulation

Four studies addressed this question: two evaluated the impact of ovarian hyperstimulation syndrome (OHSS) (59), whereas two compared multifollicular stimulation with natural cycles (60, 61). Detailed characteristics of these studies are provided in [Supplemental Table 6](#).

Fetal period, neonatal period, and early childhood. No studies specifically assessed cardiovascular or metabolic outcomes in fetuses or neonates in relation to ovarian stimulation intensity during this developmental period.

Childhood. Zhu et al. (59) compared 1,780 ART-conceived children aged 3–6 years and 83 children conceived without ART, stratified according to OHSS status and embryo transfer type (i.e., fresh-ET and FET). Children conceived after OHSS-fresh-ET had higher SBP (adjusted MD 3.193, 95% CI: 0.549–2.301) and DBP (adjusted MD 3.440, 95% CI: 0.611–2.333) than those conceived after non-OHSS-fresh-ET, whereas no blood pressure differences were observed between non-OHSS-FET and non-OHSS-fresh-ET groups (59). No adverse impact of OHSS on metabolic outcomes (glucose, lipids, BMI, and thyroid function) was observed (59).

Xu et al. (62) assessed 42 OHSS-IVF, 34 non-OHSS-IVF, and 48 children conceived without ART at age 4.5 years. Compared with both control groups, OHSS-IVF children exhibited impaired cardiac and vascular parameters, including a lower mitral E/A ratio (an echocardiographic marker of

impaired left ventricular diastolic function), smaller carotid artery diameters, and reduced FMD, whereas blood pressure and arterial stiffness were similar across groups.

Seggers et al. (61) reported higher SBP at age 4 years among 60 children conceived after controlled ovarian hyperstimulation compared with 47 conceived after modified natural cycle IVF/ICSI (regression coefficient $B = 14.09$, 95% CI: 5.39–22.79), whereas DBP and anthropometric measures were similar between groups. In contrast, Kuiper et al. (60) found no differences in blood pressure, heart rate, or anthropometric measures at age 9 years among 57 children conceived after controlled ovarian hyperstimulation, 47 conceived after modified natural cycle IVF/ICSI, and 66 conceived without ART by subfertile couples.

Adolescence. No studies specifically assessed cardiovascular or metabolic outcomes in adolescents in relation to ovarian stimulation.

Young adulthood and adulthood. No studies specifically assessed cardiovascular or metabolic outcomes in young adults or adults in relation to ovarian stimulation.

Global synthesis – ovarian stimulation. Evidence regarding the impact of ovarian stimulation on offspring cardiometabolic health remains limited to childhood cohorts. Available studies suggest that severe OHSS, particularly when associ-

ated with fresh-ET, may be linked to higher blood pressure and vascular alterations, including impaired endothelial function. However, these findings have not been consistently replicated, and metabolic outcomes appear largely unaffected. The underlying mechanisms remain uncertain but may involve the altered hormonal environment during early embryonic development or placental dysfunction. Further long-term studies are needed to determine whether vascular alterations observed in OHSS-exposed offspring persist into adolescence and adulthood and confer increased cardiovascular risk.

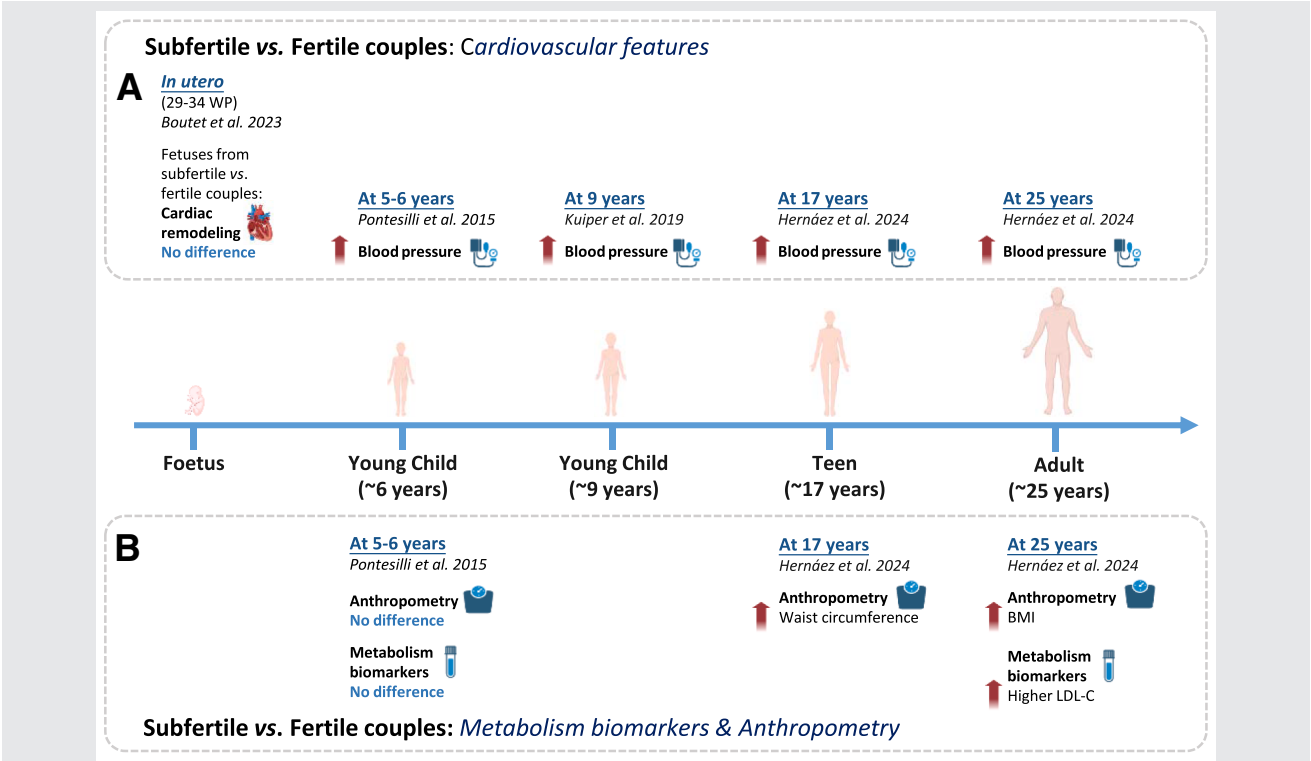
Parental infertility

For this question, a total of five studies were analyzed, detailed in the Supplemental Table 7, and synthesized in the Figure 5 (63–67).

Fetal period, neonatal period, and early childhood

Cardiovascular outcomes. Boutet et al. (65) performed fetal echocardiography at 29–34 weeks in 96 IVF fetuses (fresh-ET), 97 fetuses conceived without ART from subfertile couples, and 96 fetuses conceived without ART from fertile couples. No differences in cardiac structure or function were observed between the two groups conceived without ART (65).

FIGURE 5



Developmental timeline of cardiometabolic outcomes in offspring of subfertile vs. fertile couples conceived without ART. Overview of (A) cardiovascular and (B) metabolic/anthropometric effects (except Weng’s study assessing pediatric cardiovascular diseases from the registry). BMI = body mass index; LDL-C = low-density lipoprotein cholesterol; WP = weeks of pregnancy.

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Metabolic and anthropometric outcomes. No studies specifically assessed metabolic or anthropometric outcomes in fetuses or neonates in relation to parental infertility during this developmental period.

Childhood

Cardiovascular outcomes. Pontesilli et al. (63) reported higher DBP assessed at age 5–6 years among 333 children of subfertile couples (34 conceived after OI 51 after intrauterine insemination, 28 after IVF/ICSI, and 220 without ART) compared with 2,244 children of fertile couples (adjusted difference 1.4 mmHg, 95% CI: 0.6–2.3).

Kuiper et al. (64) assessed 149 children of subfertile couples (61 conceived without ART and 88 conceived after IVF with or without controlled ovarian hyperstimulation) and 277 children of fertile couples at age 9 years. Parental subfertility was associated with higher SBP (adjusted difference +8.10 mmHg, 95% CI: 2.10–14.20) and DBP (adjusted difference +7.31 mmHg, 95% CI: 1.56–13.07). Similar findings were observed when analyses were restricted to children of subfertile couples conceived without ART (64).

Metabolic and anthropometric outcomes. Pontesilli et al. (63) additionally found higher fasting glucose levels in OI and IVF/ICSI children compared with children of fertile couples (adjusted difference: OI 0.4 mmol/L, 95% CI: 0.2–0.6; IVF/ICSI 0.2 mmol/L, 95% CI: 0.0–0.5). No differences in anthropometry were observed between the two groups.

Adolescence and young adulthood

Cardiovascular outcomes. Hernáez et al. (66) pooled data from three European prospective birth cohorts (Portugal, Netherlands, UK), including 13,217 offspring of fertile couples with 1,392 offspring of subfertile couples, all conceived without ART. Parental subfertility was associated with higher SBP at age 17 years (adjusted difference 0.93 mmHg, 95% CI: 0.044–1.81), although this difference attenuated with age (66). By age 25 years, higher DBP (adjusted difference 1.21 mmHg, 95% CI: 0.003–2.43) and a trend toward higher LDL-cholesterol (4.07%, 95% CI: –0.79–8.93) were observed among offspring of subfertile couples (66).

Weng et al. (67) conducted a large population-based cohort study in Taiwan of children aged 0–13 years and found that parental fertility status and IVF use were independently associated with risk of pediatric cardiovascular disease. Children of subfertile couples had higher cardiovascular diagnoses regardless of ART use (67).

Metabolic and anthropometric outcomes. Hernáez et al. (66) additionally found that by age 17 years, offspring of subfertile couples had higher waist circumference (adjusted difference 1.05 cm, 95% CI: 0.11–1.99). By age 25 years, parental subfertility was associated with higher BMI (difference in mean predicted levels 1.09 kg/m², 95% CI: 0.68–1.50) (66).

Young adulthood and adulthood. The findings from Hernáez et al. (66) at age 25 years, described above, represent the most comprehensive evidence regarding the effects of parental infertility on offspring cardiometabolic health in young adulthood, with higher BMI, elevated DBP, and a trend

toward higher LDL-cholesterol in offspring of subfertile couples.

Global synthesis – parental infertility. Parental subfertility appears to contribute independently to cardiometabolic risk from childhood to young adulthood. In contrast, fetal cardiac remodeling and functional impairments observed in IVF fetuses are not detected in fetuses conceived without ART from subfertile couples, suggesting that these early cardiac alterations are primarily attributable to ART procedures rather than parental infertility itself. From childhood onward, however, parental subfertility is associated with higher blood pressure and fasting glucose levels regardless of conception mode, supporting an independent contribution of infertility-related factors to offspring cardiometabolic health. These differences may persist into adolescence and young adulthood, with reports of higher BMI, waist circumference, DBP, and LDL-cholesterol. Registry-based studies further support an association between parental fertility status and offspring cardiovascular disease risk (36). Collectively, these findings emphasize the importance of including offspring conceived without ART from subfertile couples as a comparator group to disentangle the respective contributions of ART procedures and parental background factors. The underlying mechanisms remain uncertain but may involve genetic susceptibility, epigenetic alterations, or adverse intrauterine environments related to parental metabolic or endocrine dysfunction.

DISCUSSION

In contrast to previous quantitative syntheses that primarily aimed to estimate the overall cardiometabolic risk associated with ART, the present review sought to provide a more integrated developmental perspective of cardiometabolic health across the lifespan. This systematic review used a narrative and mechanism-oriented synthesis to explore whether specific developmental periods may represent heightened windows of susceptibility and to provide a more nuanced interpretation of the respective contributions of ART procedures, including fertilization method, embryo freezing, embryo biopsy, or OHSS, and underlying parental infertility in shaping offspring cardiometabolic trajectories.

Overall, the findings reveal a complex and age-dependent pattern: subtle cardiovascular differences, including mild cardiac remodeling, modestly elevated blood pressure, and early endothelial dysfunction, are more frequently reported from fetal life through adolescence, whereas metabolic differences such as insulin resistance and adiposity remain inconsistently observed across studies. By adulthood, most parameters appear to normalize, with limited evidence of persistent cardiometabolic abnormalities. Importantly, most observed cardiovascular and metabolic differences remain within normal physiological ranges, raising the question of whether these subtle alterations are sufficient to result in clinically significant disease later in life. Although developmental programming mechanisms provide a plausible biological explanation for these findings,

their pathological relevance later in life remains uncertain. Similar alterations have also been reported among offspring of subfertile parents conceived without ART, highlighting the contribution of parental infertility to the observed associations.

Overall, the findings regarding blood pressure are broadly aligned with the recent meta-analysis by Yeung et al. (68), although also highlighting the complexity and heterogeneity of cardiovascular phenotypes observed after ART. Although Yeung et al. (32) did not identify a statistically significant overall increase in SBP or DBP among ART-conceived offspring, the investigators themselves emphasized substantial heterogeneity across studies, including differences in blood pressure measurement protocols, ART populations, and longitudinal follow-up strategies. In addition, subgroup analyses according to embryo transfer strategy (fresh-ET vs. FET) could not be adequately explored because many studies did not specify the proportion of fresh vs. frozen transfers. Several independent cohorts nevertheless consistently reported higher blood pressure values in ART offspring. Importantly, most reported blood pressure differences were modest in magnitude, which may reduce the ability of pooled analyses to detect subtle but biologically meaningful effects. Moreover, aggregation of heterogeneous ART procedures, embryo transfer strategies, developmental periods, parental infertility etiologies, and age groups at assessment may dilute specific vulnerable phenotypes or age-dependent susceptibility patterns. This may be particularly relevant given that the present review specifically aimed to explore developmental trajectories and procedure-specific contexts, including fertilization method, embryo freezing, embryo biopsy, OHSS, and underlying parental infertility. Thus, the absence of a significant pooled effect should not necessarily be interpreted as evidence for the complete absence of cardiovascular programming differences after ART.

The age-dependent nature of observed differences may partly explain these discrepancies and represents a major finding of the present review. Fetal and childhood studies more frequently report cardiovascular alterations, whereas adult studies are generally reassuring. This pattern may reflect developmental plasticity and compensatory mechanisms that normalize cardiovascular function over time. Alternatively, it may reflect differences in study design, sample size, or outcome measurement between pediatric and adult studies. Longer follow-up into middle and older adulthood is needed to determine whether early-life differences predict later cardiovascular disease. Although these differences tend to attenuate with age, their clinical relevance warrants careful consideration. As highlighted by Guo et al. (69), even modest increases in blood pressure during childhood may translate into a substantial increase in the population-level risk of stroke and coronary heart disease in adulthood.

It is also possible that early cardiovascular alterations reflect developmental adaptations or transient vascular remodeling phenomena that may not necessarily persist as overt hypertension in adulthood, but could still influence long-term cardiovascular susceptibility.

Several mechanisms may underlie observed associations between ART and offspring cardiometabolic health.

Our review found no consistent evidence that ICSI confers additional cardiometabolic risk beyond standard IVF. This is reassuring, given the widespread use of ICSI and the more invasive nature of the procedure compared with conventional IVF. Fresh-ET after ovarian hyperstimulation was occasionally associated with higher childhood blood pressure, whereas FET offspring generally exhibited normal cardiometabolic parameters. These findings suggest that the supraphysiological estrogen and progesterone levels during fresh embryo transfer may influence fetal programming, and offspring cardiovascular development, although more research is needed. Current evidence remains insufficient to determine the potential impact of endometrial preparation protocols during FET, including hormonally substituted (hormone replacement therapy/programmed) vs. natural-cycle FET, on long-term offspring cardiometabolic health. Although some signals, such as higher birth weight or an increased likelihood of large for gestational age infants, have been observed in programmed cycles (52), long-term follow-up data are still scarce.

The study assessing PGT safety at the blastocyst stage found no significant metabolic differences in offspring born from biopsied embryos, which is reassuring (57). Preimplantation genetic testing deserves special consideration as a potential confounder. It is frequently performed in fertile couples who undergo ART primarily for genetic testing purposes (e.g., carriers of monogenic disorders or chromosomal translocations) rather than because of infertility, as was the case in two (55, 56) of the three studies included in our review. This creates a unique comparison group that differs fundamentally from typical ART patients. Couples undergoing PGT may have normal fertility, younger maternal and paternal age, and different genetic backgrounds compared with infertile couples undergoing standard IVF/ICSI (56). Therefore, studies comparing PGT offspring with standard ART offspring may reflect differences in parental characteristics rather than effects of embryo biopsy per se. This “confounding by indication” complicates the interpretation of PGT safety data.

A major strength of this review is the inclusion of studies involving offspring of subfertile parents conceived without ART. The similarity of their cardiometabolic profiles to those of ART-conceived offspring suggests that parental infertility itself contributes to offspring phenotype. Parental infertility is associated with multiple factors that may independently affect offspring health. Subfertile couples are older on average, have higher rates of metabolic syndrome, obesity, and cardiovascular disease, and may carry genetic or epigenetic variants related to both infertility and cardiometabolic risk (70–72). Polyendocrine metabolic ovarian syndrome, formerly referred to as polycystic ovary syndrome, a common cause of infertility, is itself associated with insulin resistance and cardiovascular risk, which may be transmitted to offspring through genetic, epigenetic, or intrauterine mechanisms (73).

Including offspring of subfertile parents conceived without ART as a comparator group is essential to distinguish

procedure-related effects from parental background factors. Failure to account for parental subfertility may overestimate the contribution of ART procedures, a methodological challenge increasingly recognized in ART offspring research (74).

Although observational human studies cannot establish causality, experimental animal models provide important mechanistic insights into the biological pathways potentially linking ART procedures with long-term cardiometabolic health. These models are particularly informative because they allow control for parental infertility, standardization of ART procedures, and longitudinal assessment throughout the lifespan. They therefore offer a valuable framework for interpreting the subtle cardiovascular and metabolic differences observed in ART-conceived offspring. The biological plausibility of these associations is reinforced by the fact that ART procedures occur during critical windows of embryonic development and epigenetic reprogramming. Experimental studies have shown that ovarian stimulation, embryo culture conditions, cryopreservation, and embryo manipulation can influence deoxyribonucleic acid (DNA) methylation patterns, gene expression, placental development, and offspring physiology (3). In humans, ART has been associated with an increased risk of certain imprinting-related disorders, including neonatal diabetes mellitus (75), suggesting that early developmental perturbations may have long-term consequences.

Consistent with the Developmental Origins of Health and Disease paradigm, several animal studies have demonstrated cardiovascular alterations after ART. Rexhaj et al. (76) reported endothelial dysfunction, arterial hypertension in IVF-conceived mice, together with dysmethylation of the endothelial nitric oxide synthase (eNOS) promoter. Under a high-fat diet challenge, these abnormalities were associated with a 25% reduction in lifespan. The investigators proposed that these alterations could be related to the embryonic environment, potentially resulting from the combined effects of ovarian stimulation and ART procedures. Further supporting a vascular origin of these phenotypes, Meister et al. (77) demonstrated hypomethylation of the *At1bR* promoter, resulting in an increased AT1R/AT2R ratio and enhanced vascular responsiveness to angiotensin II, suggesting that altered renin-angiotensin signaling may represent an important mechanism contributing to ART-induced hypertension in mice.

Cardiac alterations have also been reported. Wang et al. (78) observed sustained upregulation of genes involved in renin-angiotensin signaling and extracellular matrix remodeling (AGTR1, CTGF, and COL3), accompanied by persistent micro ribonucleic acid (microRNA) dysregulation and altered DNA methylation patterns. More recently, Zhang et al. (5) reported left ventricular hypertrophy associated with elevated SBP in IVF-conceived mice. Notably, these structural cardiac differences diminished with advancing age, suggesting that some ART-associated cardiovascular alterations may be transient and age-dependent rather than progressive. Experimental evidence also supports long-term metabolic effects, although these appear to be strongly influenced by environmental exposures. Cerny et al. (79) reported normal glucose tolerance and insulin sensitivity in

ART-conceived mice under standard dietary conditions, whereas a high-fat diet unmasked exaggerated obesity, hyperinsulinemia, and insulin resistance. These findings suggest that ART-related biological alterations may remain clinically silent under physiological conditions and become apparent only when additional metabolic stressors are encountered later in life.

Taken together, these experimental data provide mechanistic support for the vascular, cardiac, and metabolic differences reported in human ART-conceived offspring and identify altered programming of the nitric oxide pathway, the renin-angiotensin system, and epigenetic regulatory networks as plausible biological mechanisms. Importantly, several animal studies suggest that cardiovascular phenotypes evolve across the lifespan, with early structural abnormalities partially resolving with age despite evidence of persistent molecular and vascular alterations.

This observation closely mirrors the age-dependent pattern observed in the clinical literature summarized in the present review, where cardiovascular differences are most consistently reported during fetal life, childhood, and adolescence, whereas studies conducted in young adults generally describe more reassuring cardiometabolic profiles. The convergence of experimental and clinical data therefore supports the hypothesis that at least some ART-associated cardiovascular differences may represent developmental adaptations established during early life rather than progressive cardiovascular pathology. Nevertheless, whether these early-life alterations remain clinically benign or influence susceptibility to cardiovascular disease later in adulthood remains uncertain and warrants continued long-term follow-up.

Several large-scale registries and cohort studies are ongoing and will provide valuable long-term data on ART offspring health. The European Register of Children conceived by Assisted Reproduction (EuReCa) and national ART registries in countries such as Denmark, Sweden, and Australia are collecting comprehensive health data on ART offspring. These registries will enable assessment of cardiovascular and metabolic outcomes into middle and older adulthood, when clinical disease typically manifests. Linkage of ART registries with national health databases will also allow assessment of hard clinical endpoints (myocardial infarction, stroke, diabetes) rather than surrogate markers.

Limitations

This review has several limitations. First, marked heterogeneity across studies in design, ART modalities, offspring ages, outcome definitions, and measurement methods precluded meta-analysis. Second, most studies had small to moderate sample sizes and variable follow-up durations, limiting statistical power and long-term conclusions. Third, incomplete adjustment for confounders, particularly parental infertility status, socioeconomic status, and lifestyle factors, limits causal inference. Fourth, most studies focused on childhood and adolescence; adult data remain scarce. Fifth, restriction to English-language publications may introduce language bias. Sixth, although the NOS

demonstrated high overall study quality (mean score 7.9/9; 72% Good), we did not apply a formal grading of recommendations, assessment, development, and evaluations assessment of evidence certainty, which limits our ability to provide graded recommendations. Sixth, publication bias may favor studies reporting positive associations over null findings, although our qualitative assessment did not reveal obvious patterns suggestive of selective reporting. Finally, the interpretation of long-term cardiometabolic outcomes should also consider the major changes in ART practice over time. Most adolescents and adults included in the available literature were conceived after cleavage-stage embryo transfer and, when applicable, embryo cryopreservation by slow freezing. In contrast, current ART increasingly relies on blastocyst culture, vitrification, and individualized ovarian stimulation strategies, including freeze-all approaches to minimize exposure to supraphysiological hormonal environments. In addition, considerable variability exists across countries and centers with respect to stimulation protocols, culture media, embryo culture duration, cryopreservation techniques, the use of PGT, and laboratory practices. As a result, findings derived from older ART cohorts may not be fully generalizable to offspring conceived using contemporary procedures, and procedural heterogeneity may have contributed to the variability of findings observed across studies. This temporal gap highlights the need for continued follow-up of more recent ART cohorts to determine whether the cardiometabolic profiles observed in earlier generations persist under current clinical practices.

Future research would benefit from large prospective ART registries with follow-up extending into later adulthood, enabling assessment of clinically relevant outcomes such as cardiovascular disease and type 2 diabetes. The development of standardized core outcome sets for cardiometabolic health would also improve comparability across studies, reduce methodological heterogeneity, and strengthen future evidence synthesis.

These findings provide reassurance that ART-conceived offspring do not exhibit major cardiometabolic abnormalities in adulthood, although subtle early-life differences warrant continued surveillance. Clinicians should counsel ART families that observed differences are generally mild, age-dependent, and likely multifactorial rather than solely procedure-related. The contribution of parental infertility underscores the importance of preconception counseling and optimization of parental health (weight management, glycemic control, cardiovascular risk factor modification) for all couples seeking fertility treatment.

CONCLUSION

The ART-conceived offspring may exhibit subtle, age-dependent cardiovascular differences from fetal life through adolescence, with most parameters normalizing by adulthood (a summary provided in the [Supplemental Fig. 1](#), available online). Metabolic differences are inconsistently reported. Importantly, parental infertility appears to contribute substantially to observed associations, highlighting the need for study designs that disentangle procedure-related effects

from parental background. Long-term follow-up into middle and older adulthood is needed to determine whether early-life differences predict later cardiovascular disease.

CRediT Authorship Contribution Statement

Julie Firmin: Writing – review & editing, Validation, Investigation, Data curation. **Myriam Slama:** Writing – original draft, Visualization, Resources, Investigation, Data curation. **Lucile Ferreux:** Writing – review & editing. **Céline Chalas:** Writing – review & editing. **Véronique Drouineaud:** Writing – review & editing. **Khaled Pocate-Cheriet:** Writing – review & editing. **Ahmed Chargui:** Writing – review & editing. **Virginie Barraud-Lange:** Writing – review & editing. **Catherine Patrat:** Writing – review & editing, Validation, Supervision. **Patricia Fauque:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of Interests

J.F. has nothing to disclose. M.S. has nothing to disclose. L.F. has nothing to disclose. C.C. has nothing to disclose. V.D. has nothing to disclose. K.P-C has nothing to disclose. A.C. has nothing to disclose. V.B-L has nothing to disclose. C.P has nothing to disclose. P.F. has nothing to disclose.

SUPPLEMENTAL MATERIAL

Supplemental data for this article can be found online at <https://doi.org/10.1016/j.fertnstert.2026.06.031>.

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