ESC European Society of Cardiology

European Heart Journal (2025) **46**, 687–698
https://doi.org/10.1093/eurheartj/ehae886

***FAST*TRACK – CLINICAL RESEARCH**
Epidemiology, prevention, and health care policies

Cardiovascular safety of assisted reproductive technology: a meta-analysis

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Received 27 April 2024; revised 12 September 2024; accepted 6 December 2024; online publish-ahead-of-print 23 December 2024

See the editorial comment for this article 'Whether women undergoing assisted reproductive technologies have an increased risk of cardiovascular disease remains an unanswered question', by M.C. Magnus, https://doi.org/10.1093/eurheartj/ehae910.

Abstract

Background and Aims The increasing use of assisted reproductive technology (ART) has raised concerns regarding its long-term cardiovascular safety due to potential hormonal imbalances and pro-thrombotic states. This study aimed to assess the long-term cardiovascular risk associated with fertility treatments in women.

Methods Following PRISMA guidelines, a systematic review and meta-analysis was conducted in MEDLINE (via PubMed) from inception to January 2024. Randomized, cohort, or case-control studies were included if fulfilling the following criteria: the association between ART and the subsequent cardiovascular outcome was reported and adjusted for confounding factors (at least age); the presence of a control group; and minimum 1-year follow-up. Effect size (ES) estimates of the association between fertility therapy and subsequent cardiovascular disease were pooled using the DerSimonian and Laird random-effects model. Heterogeneity was assessed with the I^2 index. This study is registered on PROSPERO (CRD42024505605).

Results Of the 7298 articles screened, 10 studies were included, encompassing 500 664 women undergoing ART and 36 395 240 controls. The analysis found no significant increase in the long-term risk of major adverse cardiovascular events [ES 1.04, 95% confidence interval (CI) 0.88–1.23, I^2 87.61%, $P = .63$], coronary heart disease (ES 0.88, 95% CI 0.71–1.10, I^2 24.36%, $P = .26$), stroke (ES 1.21, 95% CI 0.92–1.59, I^2 70.40%, $P = .17$), venous thromboembolism (ES 0.95, 95% CI 0.70–1.28, I^2 49.13%, $P = .73$), hypertension (ES 1.08, 95% CI 0.88–1.32, I^2 94.63%, $P = .46$), or diabetes (ES 1.03, 95% CI 0.86–1.22, I^2 78.44%, $P = .77$). Assisted reproductive technology was associated with a lower risk of heart failure (ES 0.75, 95% CI 0.60–0.94, I^2 0.00%, $P = .01$).

Conclusions Assisted reproductive technology use does not appear to be significantly associated with an increased long-term risk of cardiovascular diseases in women. While these findings suggest the cardiovascular safety of fertility treatments, further research is warranted.

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Structured Graphical Abstract

Key Question

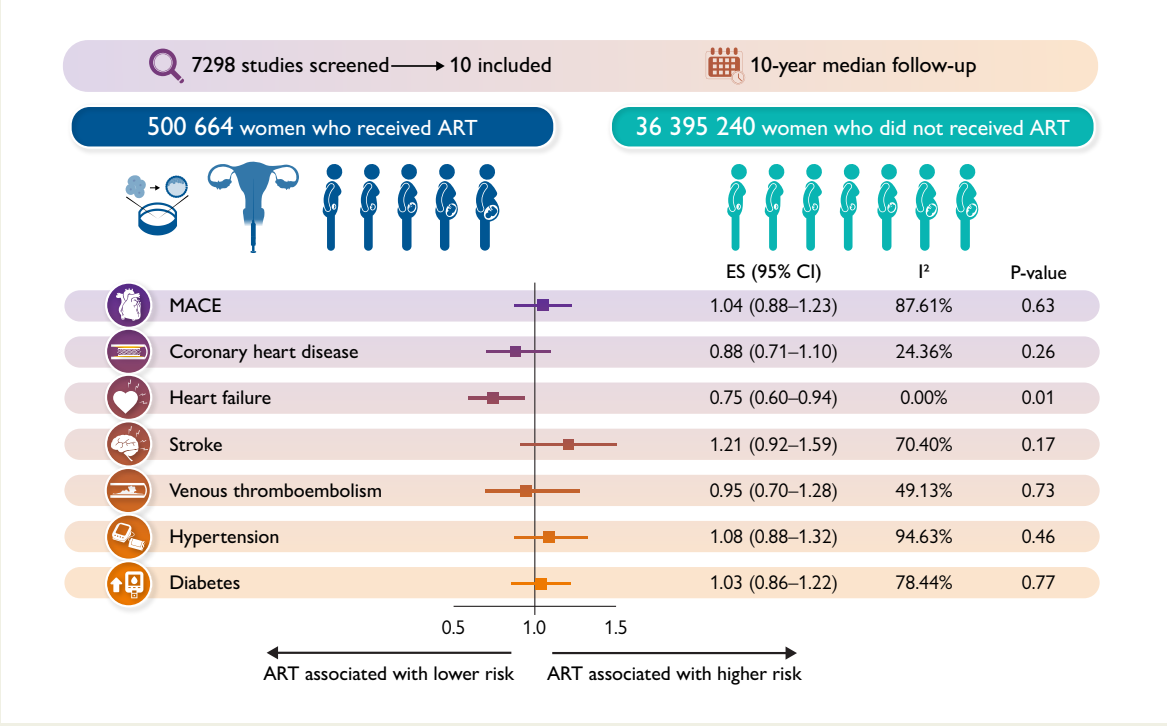
The increasing use of assisted reproductive technology (ART) has raised concerns regarding its long-term cardiovascular safety due to potential hormonal imbalances and pro-thrombotic states.

Key Finding

This meta-analysis, encompassing data from 500 664 women undergoing ART and 36 395 240 controls, found that ART use was not associated with an increased risk of cardiovascular diseases in women over a median follow-up of ten years.

Take Home Message

Although these findings indicate that fertility treatments are generally safe for long-term cardiovascular health, further research is needed to explore the safety of specific ART techniques.



Systematic review and meta-analysis evaluating the association between assisted reproductive technology (ART) and cardiovascular risk in women. ART, assisted reproductive technology; CI, confidence interval; ES, effect size; MACE, major adverse cardiovascular events.

Keywords Assisted reproductive technology • Cardiovascular disease • *In vitro* fertilization • Metabolic disease • Meta-analysis • Systematic review

Introduction

The use of assisted reproductive technology (ART), including *in vitro* fertilization (IVF), intrauterine insemination, and ovarian stimulation, has significantly increased, now accounting for as much as 4% of pregnancies worldwide.[1] Prior studies have highlighted increased maternal morbidity in pregnancies achieved through fertility treatments compared with natural conception.[2] Assisted reproductive technology has been associated with a higher risk of placenta accreta spectrum and consequent need for transfusion, a higher rate of twin pregnancies, and a higher likelihood of subsequent hospitalization.[3] Of note, certain ART stimulation protocols that elevate exogenous oestrogen levels may induce a pro-thrombotic state and disrupt the renin-angiotensin-aldosterone system, potentially causing endothelial damage and increased risk of gestational hypertension and pre-eclampsia.[4,5] This correlation is of particular concern considering that women who experience pre-eclampsia face a two-fold increase in the risk of developing cardiovascular disease later in life.[6] Furthermore, there is growing apprehension regarding a potential increase in the occurrence of stroke following ART.[7,8]

Cardiovascular disease stands as the predominant cause of mortality among women, responsible for one-third of all female deaths.[9] Women with cardiovascular disease have poorer outcomes compared with men with the same condition, compounded by the alarming rise in acute myocardial infarction rates among younger women.[10] The biological reasons and sex-specific pathophysiology remain elusive, underscoring the importance of exploring non-traditional risk factors, including exogenous reproductive hormones and fertility-related issues as contributors to future cardiovascular events.[11] As a result, this field of research is rapidly evolving, with new studies emerging annually.

Dayan *et al.*[8] provided a summary of the evidence up to 2017; however, the very limited number of available studies precluded definitive conclusions. To address this critical gap, we conducted an updated systematic review and meta-analysis, incorporating recent evidence, to better understand the long-term implications of ART on women's cardiovascular health.

Methods

We registered the protocol of the study on PROSPERO (CRD42024505605), and we followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.[12]

Search strategy

We performed a systematic literature search of English language publications in MEDLINE (via PubMed) from inception until January 2024. We also conducted backward citation tracking (i.e. reviewing references from identified articles and pertinent reviews). The search strategy can be found in the Supplementary data.

Study selection

We included randomized, cohort, or case-control studies fulfilling the following criteria: (i) the association between fertility therapy and the subsequent cardiovascular outcome was reported and adjusted for confounding factors (at least age); (ii) the presence of a control group; and (iii) minimum 1-year follow-up. We excluded (i) case reports, reviews, meta-analyses, letters, and editorials; (ii) studies on non-human beings; and (iii) non-English language publications. Two independent authors (A.C.L. and M.C.) evaluated all citations by titles, abstracts, and full-text papers. Disagreements between reviewers were settled by consulting G.S. and N.D.S.

Assisted reproductive technology definition

Assisted reproductive technology was defined as the use of a fertility treatment, including ovarian stimulation drugs (gonadotropin-releasing hormone agonist or antagonist), clomiphene citrate, or ovulation induction drugs (letrozole). We included IVF-based as well as non-IVF–based approaches (e.g. intrauterine insemination and isolated ovulation induction) to achieve pregnancy. We defined a comparison group as women who did not receive fertility therapy, regardless of baseline infertility or whether they ever became pregnant.

Outcomes of interest

We evaluated the incidence of cardiovascular events and metabolic diseases known to be cardiovascular risk factors, i.e., a composite endpoint of major adverse cardiovascular event (MACE), coronary heart disease (including acute or chronic coronary syndrome), heart failure, cerebrovascular events (including cerebral venous thrombosis, ischaemic stroke, haemorrhagic stroke, or transient ischaemic attack), stroke (including ischaemic or haemorrhagic stroke), venous thromboembolism (including pulmonary embolism or deep vein thrombosis), diabetes, and hypertension. Supplementary data online, *Table S1* provides the specific definitions for each outcome by the corresponding study.

Quality assessment

The quality assessment was performed using the Risk Of Bias In Non-Randomized Studies - of Interventions (ROBINS-I), which evaluates the risk of bias in the main domains of non-randomized studies that compare the health effects of two or more interventions. Among a total of seven domains, the first two (confounding and selection of participants in the study) occur pre-intervention, the third (classification of the interventions) happens at intervention, and the remaining four (deviations from intended interventions, missing data, measurement of outcomes, and selection of the reported result) are post-intervention.[13] The quality assessment is outcome-specific and is graded according to the following categories: 'low', 'moderate', 'serious', and 'critical' risk of bias. 'Low risk' corresponds to the risk of bias in a 'high-quality' randomized trial. The judgements within each domain carry forward an overall risk of bias judgement for the assessed outcome.

Data analysis

Depending on the included studies, the adjusted risk ratio (RR), odds ratio (OR), and hazard ratio (HR) with their 95% confidence intervals (CIs) were extracted and used as effect size (ES) estimates of the association between fertility therapy and subsequent cardiovascular disease. Pooled ESs with 95% CIs were calculated using the DerSimonian and Laird random-effects model. The heterogeneity among the studies was evaluated using the Cochrane Q test based on a χ^2 distribution and the I^2 test to evaluate inconsistencies. A value of 0% indicates no observed heterogeneity, and values of ≤25%, ≤50%, and >50% indicate low, moderate, and high heterogeneity, respectively. Publication bias and small-study effects were evaluated visually using funnel plots. The Egger test was then applied to formally assess the symmetry of these plots. The trend in the estimates of the overall ESs according to follow-up duration was evaluated with a cumulative meta-analysis. Based on these findings, we performed a *post hoc* subgroup analysis on the risk of MACE, stratifying by follow-up duration (≤5 years vs. >5 years). The interaction between the subgroup and the ES was evaluated with a random-effects meta-regression analysis. For sensitivity analysis, we limited inclusion to studies specifically assessing IVF and conducted a leave-one-out analysis, iteratively removing one study at a time to ensure that no single study drove our findings for any of the endpoints. The two-sided level of significance was denoted as $P < .05$. Statistical analyses were conducted using Stata (version 17; Stata Corp, College Station, TX, USA).

Results

Search results and characteristics of included studies

The search strategy identified 7298 studies. Seven thousand and two hundred eighty-eight were excluded as they did not meet the inclusion criteria (details in Supplementary data online, *Figure S1*). Full-text articles from 10 studies[7,14–22] were assessed for eligibility and included in the qualitative and quantitative analysis. Their key features are summarized in *Table 1* and Supplementary data online, *Tables S1* and *S2*. The included studies were published between January 2013 and January 2024 and had a median follow-up of 10 years [interquartile range (IQR) 5–11 years). Most of them were retrospective cohort studies ($n = 6$).[7,15,19–22] One was a nested case-cohort study that resulted in two publications assessing different outcomes.[14,16] One was a prospective cohort study,[17] and the last one was an observational analysis of cardiovascular events of a randomized trial evaluating electrocautery of ovaries vs. gonadotropins in women with clomiphene resistant polycystic ovarian syndrome.[18] *In vitro* fertilization was the most commonly used ART across the studies, while seven studies also included other ART methods such as intrauterine insemination and ovarian induction.[7,14,18–20,22] Most studies did not adjust for critical confounders, such as education, smoking, and body mass index/obesity (see Supplementary data online, *Table S2*). In cases where adjustments were made, confounders were typically handled as binary variables (e.g. obese vs. non-obese). These limitations allow for residual confounding, which may significantly increase the potential and magnitude of bias in the findings.

Characteristics of women included

We included a total of 500 664 women who received ART and 36 395 240 women who did not (details in *Table 2*). Women who underwent ART were older [33 (IQR 31–34) vs. 32 (IQR 29–33)]

Table 1 Characteristics of the included studies

Study	Design	Population	ART	Control	Country	Ethnicity
Udell *et al.*[15]	Retrospective cohort	Women who delivered between 1993 and 2010	IVF, IUI, or OI	No IVF, IUI, or OI	Canada	Not specified
Henriksson *et al.*[14]	Case-cohort	Women who delivered between 1990 and 2008	IVF	No IVF	Sweden	Caucasian
Westerlund *et al.*[16]	Case-cohort	Women who delivered between 1990 and 2008	IVF	No IVF	Sweden	Caucasian
Farland *et al.*[17]	Prospective cohort	Women who reported use of fertility treatment or incident infertility between 1993 and 2009	IVF	Women with infertility issues who did not use IVF, IUI, or OI	USA	Mixed
Ben-Yaakov *et al.*[19]	Retrospective cohort	Women who delivered between 1988 and 2012	IVF or OI	No IVF or OI	Israel	Mixed
Nahuis *et al.*[18]	Long-term follow-up of randomized trial	Women with PCOS resistant to clomiphene citrate who were randomized to OI or electrocautery of the ovaries between 1998 and 2011	OI	Electrocautery of ovaries	Netherlands	Caucasian
Farland *et al.*[20]	Retrospective cohort	Women who delivered between 2004 and 2017	ART	Fertile women	USA	Mixed
Magnus *et al.*[21]	Retrospective cohort	Women who delivered between 1984 and 2015	IVF, ICSI, or ET	No IVF, ICSI, or ET	Scandinavian countries	Caucasian
Sachdev *et al.*[7]	Retrospective cohort	Women who delivered between 2010 and 2018	IVF, IUI, or OI	No IVF, IUI, OI, fertility preservation, or gestational carrier	USA	Mixed
Wei *et al.*[22]	Retrospective cohort	Women who delivered between 2008 to 2019	ART	No ART	Canada	Mixed

ART, assisted reproductive technologies; ET, embryo transfer; ICSI, intracytoplasmic sperm injection; IVF, *in vitro* fertilization; IUI, intrauterine insemination; OI, ovulation induction; PCOS, polycystic ovary syndrome.

Table 2 Women characteristics in the included studies according to the presence or absence of fertility therapy

	Udell et al.[15]		Henriksson et al.[14]		Westerlund et al.[16]		Farland et al.[17]		Ben-Yaakov et al.[19]		Nahuis et al.[18]		Farland et al.[20]		Magnus et al.[21]		Sachdev et al.[7]		Wei et al.[22]	
	ART	Control	ART	Control	ART	Control	ART	Control	ART	Control	ART	Control	ART	Control	ART	Control	ART	Control	ART	Control
N	6979	1 179 774	23 498	116 960	23 498	116 960	7211	8261	4153	95 138	69	69	27 082	448 227	97 474	2 398 967	287 813	31 052 178	22 887	978 706
F-UP (years)*	10		1		9		>20		12		10		4		11		1		11	
Age at delivery	34 (31–36)	29 (25–33)	33 ± 4	33 ± 4	33 ± 4	33 ± 4	44 ± 4.	46 ± 4.5	31 ± 6	29 ± 6	29 (4)	28.5 (4)	36 ± 4.5	32 ± 5	29 ± 5	34 ± 5	32 (28–36)	28 (23–32)	NA	NA
DM	2.2%	1.5%	NA	NA	NA	NA	NA	NA	14.1%	6.2%	NA	NA	9.03%	6.00%	0.7%	0.6%	NA	NA	NA	NA
Hypertension	3.1%	2.5%	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	3.93%	2.30%	1.2%	0.8%	5.1%	2.0%	NA	NA
Dyslipidaemia	3.8%	2.5%	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Smoking	NA	NA	NA	NA	14.3%	17.1%	36%	34%	NA	NA	NA	NA	NA	NA	6.3%	13.8%	NA	NA	NA	NA
Obesity	NA	NA	NA	NA	8.1%	8.2%	NA	NA	2.0%	1.0%	NA	NA	NA	NA	6.3%	5.8%	5.9%	2.2%	NA	NA
Parity	NA	NA	100	100	100	100	5.4	0.3	1.5 ± 1.0	2.8 ± 2.0	NA	NA	NA	NA	NA	NA	NA	NA	37%	56.8%
Ovulatory disorder	NA	NA	3.4%	0.3%	3.4%	0.3%	0.13%	4.0%	NA	NA	100%	100%	NA	NA	4.0%	0.6%	NA	NA	NA	NA
Prior multiple gestation	0.2%	0.1%	16.9%	2.6%	16.9%	2.6%	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	14.2%	1.7%	NA	NA
Pre-eclampsia	7.0%	3.0%	5.3%	2.0%	5.3%	2.0%	NA	NA	9.1%	4.7%	1.0%	0%	NA	NA	10.3%	8.0%	8.7%	4.3%	7.4%	3.5%
Gestational DM	8.0%	3.0%	NA	NA	NA	NA	NA	NA	NA	NA	6.0%	4.0%	NA	NA	NA	NA	8.2%	2.0%	NA	NA
PA-VTE	NA	NA	0.4%	0.2%	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0.1%	0.03%

Values are number, rates %, mean ± SD, or median (interquartile range).
BMI, body mass index; DM, diabetes mellitus; F-UP, follow-up; PCOS, polycystic ovary syndrome; PA-VTE, pregnancy-associated venous thromboembolism.
*Follow-up duration is reported as a measure of central tendency (mean or median).

and had more ovulatory disorders, including polycystic ovary syndrome, and cardiovascular risk factors, except for smoking habit, which was more prevalent among controls. However, it is important to note that the majority of women in both groups were likely at low cardiovascular risk (i.e. <2.5% risk over 10 years) because of their sex and age and the generally low prevalence of cardiovascular risk factors.[23]

When assessed, pregnancy-related complications were more frequent in women who received fertility treatment as compared with those who did not. Such complications included pre-eclampsia, gestational diabetes, and pregnancy-associated venous thromboembolism.

Quality assessment

Quality assessment domains are summarized in Supplementary data online, *Table S3*. All the included studies were considered at 'serious risk of bias'. This was mainly due to the impact of confounding factors on the reported outcome. We did not observe the presence of small-study effects, as shown in Supplementary data online, *Figure S2* and *Table S4*.

Major adverse cardiovascular event

Nine studies reported MACE within their study outcomes among 493 453 women who received ART and 36 387 979 who did not.[7,14–16,18–22] Of these studies, three had follow-up durations of ≤5 years (ranging from 1 to 4 years, with a median of 1 year), while six had follow-up durations of >5 years (ranging from 9 to 12 years, with a median of 10.5 years). Overall, exposure to fertility therapies was not significantly associated with an increased risk of MACE (ES 1.04, 95% CI 0.88–1.23, I^2 87.61%, $P = .63$; *Figure 1*) after adjusting for confounding factors. Similar findings were observed when iteratively removing one study at a time (see Supplementary data online, *Figure S3*) or analysing only studies on IVF specifically (see Supplementary data online, *Figure S4*). However, we found evidence for significant interaction between follow-up duration and MACE risk (P for interaction = .037). Specifically, both subgroup and cumulative analysis showed that women who received ART had an elevated risk of MACE in the early years post-treatment, while this association was not evident in the analyses including studies with extended follow-up durations (*Figure 1*; Supplementary data online, *Figure S5*).

Coronary heart disease

Four studies assessed the risk of coronary heart disease, including both acute and chronic coronary syndromes among 150 838 women who received ART and 4 674 407 controls.[15,16,21,22] The overall pooled

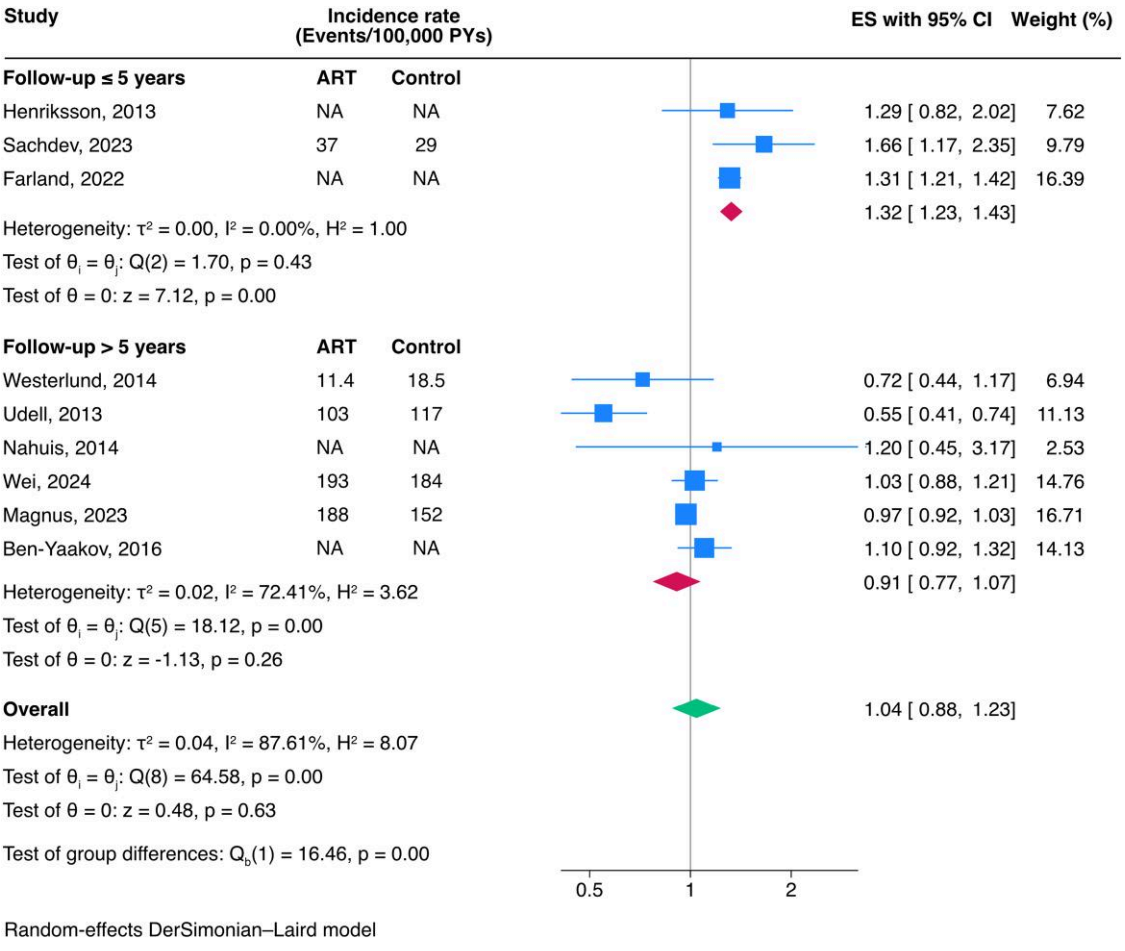


Figure 1 Risk of major adverse cardiovascular event in women receiving assisted reproductive technology and controls. Studies are grouped by follow-up duration. Pooled effect size with 95% confidence intervals was calculated using the DerSimonian and Laird random-effects model. ART, assisted reproductive technology; CI, confidence interval; ES, effect size; PY, person-year

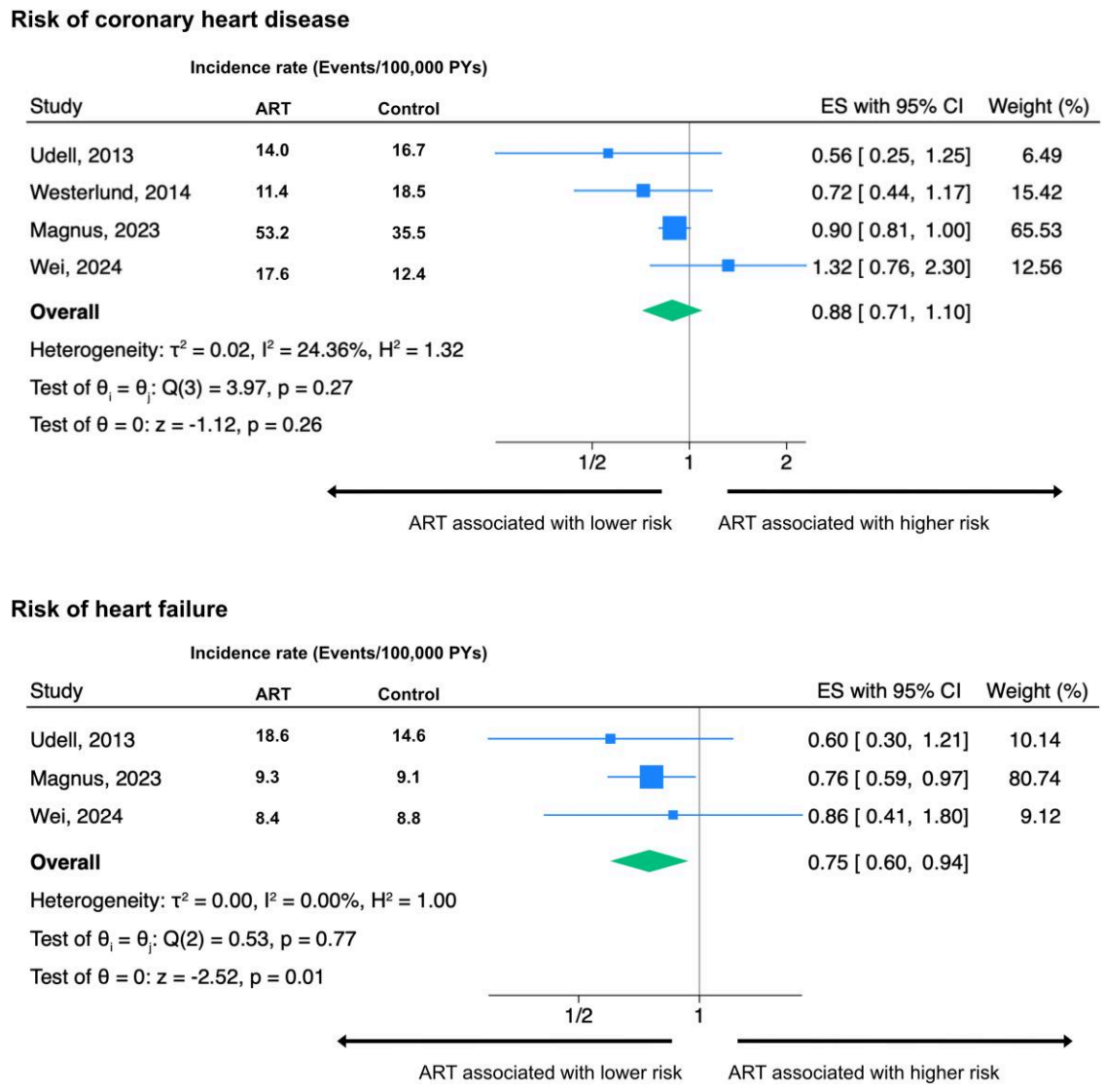


Figure 2 Risk of coronary heart disease and heart failure in women receiving assisted reproductive technology and controls. Pooled effect sizes with 95% confidence intervals were calculated using the DerSimonian and Laird random-effects model. ART, assisted reproductive technology; CI, confidence interval; ES, effect size; PY, person-year

estimate showed no significant association between ART and the subsequent risk of coronary heart disease (ES 0.88, 95% CI 0.71–1.10, I^2 24.36%, $P = .26$; *Figure 2*). Similar findings were observed when iteratively removing one study at a time (see Supplementary data online, *Figure S3*) or analysing only studies on IVF specifically (see Supplementary data online, *Figure S4*). The follow-up periods for studies assessing this outcome were highly consistent, ranging from 9 to 11 years (see Supplementary data online, *Figure S5*).

Heart failure

Three studies assessed the occurrence of heart failure among their outcomes, involving 127 340 women who received ART and 4 557 447 women who did not.[15,21,22] After adjusting for confounding factors, exposure to ART was associated with a lower risk of developing heart failure during follow-up without evidence of heterogeneity across the studies (ES 0.75, 95% CI 0.60–0.94, I^2 0.00%, $P = .01$; *Figure 2*). We could not perform the sensitivity analysis on IVF as the type of ART because it was evaluated in only one study (i.e. Magnus *et al.*[21]; ART: HR 0.76, 95% CI 0.59–0.97; IVF: HR 0.79, 95% CI 0.56–1.10). The follow-up periods for studies assessing this outcome were highly consistent, ranging from 10 to 11 years (see Supplementary data online, *Figure S5*).

Cerebrovascular events and stroke

Five studies reported on cerebrovascular events, which comprised ischaemic stroke, haemorrhagic stroke, cerebral venous thrombosis, and transient ischaemic attack.[7,15,16,21,22] A total of 438 651 women receiving fertility therapy were compared with 35 726 585 women who did not. We did not find any significant association between exposure to ART and cerebrovascular events after adjusting for confounders (ES 1.19, 95% CI 0.94–1.50, I^2 62.55%, $P = .15$; *Figure 3*). Similar findings

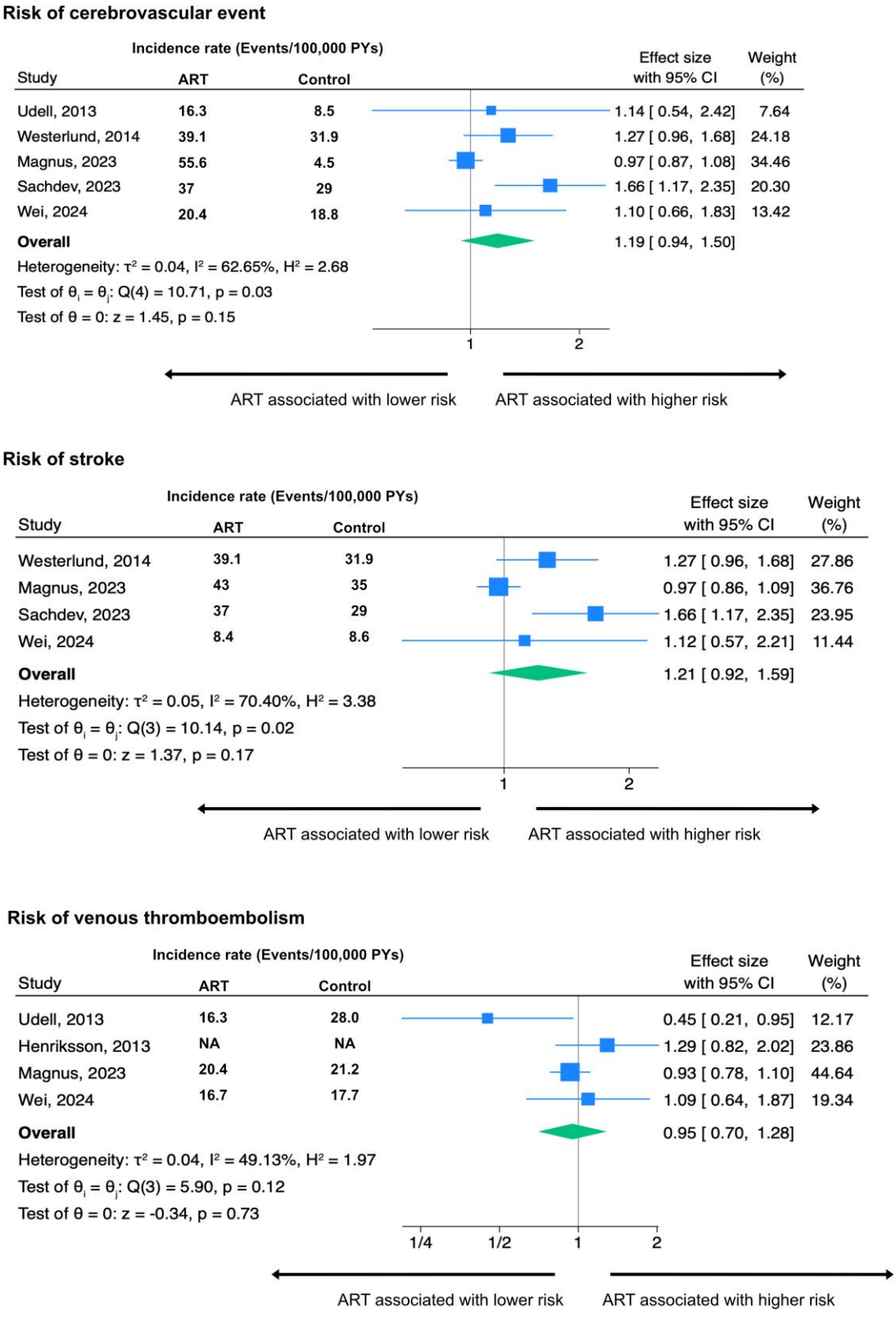


Figure 3 Risk of cerebrovascular event, stroke, and venous thromboembolism in women receiving assisted reproductive technology and controls. Pooled effect sizes with 95% confidence intervals were calculated using the DerSimonian and Laird random-effects model. ART, assisted reproductive technology; CI, confidence interval; ES, effect size; PY, person-year

were observed when analysing only studies on IVF specifically (see Supplementary data online, *Figure S4*). Cumulative and leave-one-out analysis revealed that studies with a shorter follow-up (specifically Sachdev *et al.*[7]) reported larger associations between ART and the risk of cerebrovascular event (see Supplementary data online, *Figures S3 and S5*); however, after adding studies with longer follow-up, the pooled risk of cerebrovascular event was similar between those who received ART and those who did not.

When we included the four studies specifically reporting on stroke incidence, we compared a total of 431 672 women receiving ART vs. 34 546 811 women who did not.[7,16,21,22] Similarly to cerebrovascular events, we did not reveal any association between exposure to ART and stroke after adjusting for confounders (ES 1.21, 95% CI 0.92–1.59, I^2 70.40%, $P = .17$; *Figure 3*).

Venous thromboembolism

Four studies evaluated the incidence of venous thromboembolism following fertility therapy among 150 838 women who were exposed to it and 4 674 407 women who were not.[14,15,21,22] Overall, exposure to ART was not significantly associated with a long-term risk of venous thromboembolism (ES 0.95, 95% CI 0.70–1.28, I^2 49.13%, $P = .73$; *Figure 3*), even after removing one study at a time (see Supplementary data online, *Figure S3*), analysing only studies on IVF specifically (see Supplementary data online, *Figure S4*), or accumulating them by order of follow-up duration (see Supplementary data online, *Figure S5*).

Hypertension

Five studies assessed the occurrence of long-term hypertension after ART among 87 657 women who received fertility therapy and 2 731 928 women who did not.[15–17,20,22] Exposure to ART was not significantly associated with an increased risk of long-term hypertension after adjusting for confounding factors (ES 1.08, 95% CI 0.88–1.32, I^2 94.63%, $P = .46$; *Figure 4*). We observed consistent findings after removing one study at a time (see Supplementary data online, *Figure S3*) or when assessing IVF specifically (see Supplementary data online, *Figure S4*). Cumulative analysis showed that women who received ART had a higher risk of hypertension in the first years following treatment (see Supplementary data online, *Figure S5*); however, this risk disappeared after adding studies with longer follow-up.

Diabetes

Three studies reported on the incidence of diabetes following ART, involving 57 559 women who received fertility therapy and 1 744 961 who did not.[15,16,20] The overall pooled estimate showed no significant association between exposure to ART and the development of diabetes after adjusting for confounders (ES 1.03, 95% CI 0.86–1.22, I^2 78.44%, $P = .77$; *Figure 4*). Cumulative and leave-one-out analysis revealed that studies with a shorter follow-up (specifically Farland *et al.*[20]) reported larger associations between ART and the risk of diabetes (see Supplementary data online, *Figures S3 and S5*); however, after adding studies with longer follow-up, the pooled risk of diabetes was similar between those who received ART and those who did not. We could not perform the sensitivity analysis on IVF as the type of ART because it was evaluated only by Westerlund *et al.*[16] (see *Figure 4*).

Discussion

Our comprehensive meta-analysis, encompassing observational data from 500 664 women who underwent ART compared with 36 395 240 women who did not, found no significant association between fertility treatments and long-term risk of cardiovascular diseases (*Structured Graphical Abstract*).

These findings are particularly significant in light of the higher prevalence of cardiovascular diseases and metabolic conditions, including obesity, diabetes, and polycystic ovary syndrome, among women with infertility, a trend also highlighted by the present study.[24,25] These conditions elevate the risk of cardiovascular events, potentially necessitating closer monitoring of women with fertility issues.[26,27] Our meta-analysis, including studies adjusting for these confounders, found that ART was not independently associated with a significant increase in the long-term incidence of adverse cardiovascular events.

There is growing apprehension on the risk of stroke following ART,[7,8] a concern supported by plausible biological mechanisms.[28] Infertility treatments could disrupt endogenous hormone levels, particularly with the use of agonist protocols, leading to significant haemodynamic changes, such as variations in blood pressure and heart rate.[29] Additionally, ovarian hyperstimulation syndrome, a rare but severe complication of ART, may induce a hypercoagulable state, severe multiorgan dysfunction, and considerable fluid shifts.[30] The practice of transferring multiple embryos can result in multi-foetal gestations, further complicating the pregnancy.[31–33] Infertility treatments may predispose to short-term pregnancy complications, including ischaemic placental diseases (e.g. pre-eclampsia, placental abruption, and foetal growth restriction), hypertensive disorders, and gestational diabetes.[15,34] We also found that studies with shorter follow-up reported a significantly elevated risk of cardiovascular and cerebrovascular events following ART. However, this association diminished and was no longer significant after adding studies with longer follow-up.

These findings can be interpreted through two potential frameworks. First, under the assumption of a strong causal relationship, ART may act as a trigger for MACE in women with an underlying predisposition to cardiovascular disease, manifesting in the immediate years post-treatment. This potential harm could be mediated by the physical and psychological impact of infertility treatments. Given the rarity of MACE in this young population,[23] any initial risk signal may become diluted as more events occur due to other causes, rendering the association undetectable at 10 years. This interpretation suggests that ART could indeed increase short-term MACE incidence, an effect we cannot presently exclude. Alternatively, under a weaker causal framework, the observed short-term risk elevation may reflect methodological limitations rather than a true causal effect. Insufficient adjustment for confounding factors, reverse causation, or confounding by indication could play a role; for instance, women predisposed to stressful lifestyles may independently have a higher MACE risk and opt for ART.[35]

Certain study designs could help clarify this association. For example, the six studies reporting MACE outcomes with median follow-up > 5 years could undertake additional analyses focusing on shorter-term MACE outcomes.[15,16,18,19,21,22] Among these, only Westerlund *et al.*[16] stratified outcomes by four follow-up intervals (<1 year, 1 to <5 years, 5 to <10 years, and >10 years). Although a formal analysis indicated homogeneity of HRs for diabetes, hypertension, and coronary heart disease over time, the risk of stroke showed a notable trend towards increased risk in the 1 to <5 years period (HR 1.93, 95% CI 1.25–2.97; *P*-value for homogeneity of HRs over time = .10). If other studies using similar stratified analyses also reveal a similar pattern,

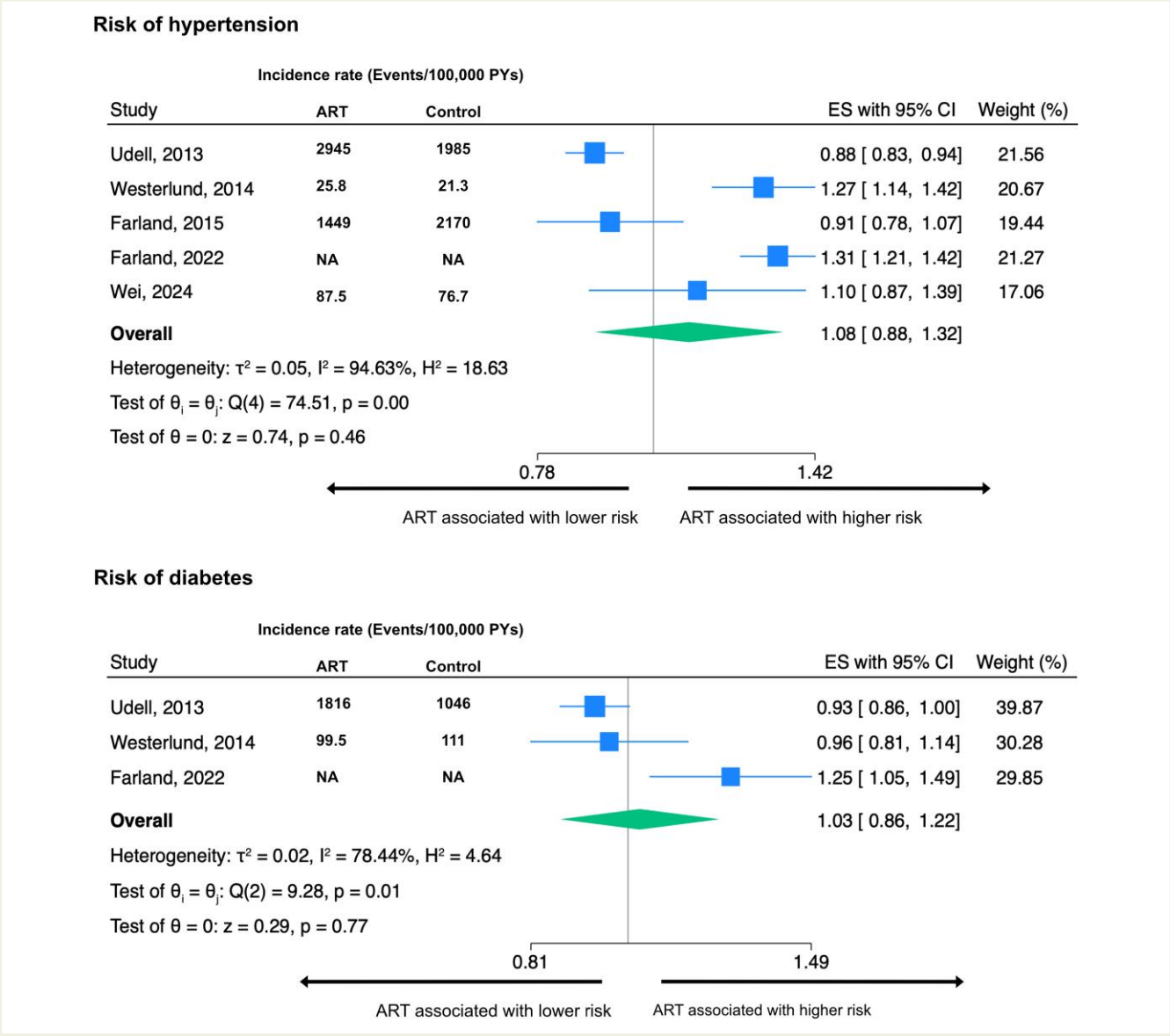


Figure 4 Risk of hypertension and diabetes in women receiving assisted reproductive technology and controls. Pooled effect sizes with 95% confidence intervals were calculated using the DerSimonian and Laird random-effects model. ART, assisted reproductive technology; CI, confidence interval; ES, effect size; PY, person-year

this would strengthen support for a causal short-term risk associated with ART. Furthermore, if effect estimates remain consistent irrespective of the confounders included in the analysis, this would provide additional evidence of a causal effect. Future analyses should therefore report both age-adjusted and fully adjusted models, allowing for a meta-analysis that examines the impact of varying adjustment levels on MACE risk.

We reported a significantly lower risk of heart failure among women who received ART, tough the biological mechanism remains elusive. We cannot exclude that intracytoplasmic sperm injection, a specific form of ART, was mainly utilized by women who were otherwise healthy and sought treatment due to an infertility of the partner. This might explain why the only study with detailed information on ART type reported a lower risk of MACE among women who had used intracytoplasmic sperm injection (HR 0.83; 95% CI 0.74–0.94), but not among those who had used IVF (HR 1.03; 95% CI 0.96–1.12), as compared with women who did not undergo ART.[21] Moreover, other selection biases might have favoured ART. Women receiving fertility therapy may be more inclined to adopt healthier behaviours, while those with unhealthy lifestyles may be less likely to seek fertility treatment.[36] Lastly, although most studies adjusted for socio-economic factors, we cannot rule out the influence of residual, unmeasured socio-economic confounders linked to higher ART utilization and lower cardiovascular disease risk.

Strengths and limitations

The primary limitation of this meta-analysis is the insufficient detail about ART used, such as whether intrauterine cytoplasmic sperm injection or IVF and embryo transfer was employed, the choice between fresh or frozen embryo or blastocysts, and number of cycles before

obtaining a pregnancy. This lack of granularity precluded us from evaluating the different ART types. Nonetheless, our sensitivity analysis on the IVF subgroup yielded consistent results. Further research is required to evaluate the cardiovascular safety profile of each IVF method, including fresh vs. frozen embryo transfer. Additionally, we were unable to stratify our population by subgroups of interest, such as cardiovascular risk categories.

A second limitation stems from the retrospective design of the included studies, most of which were based on population registries and thus lacked detailed data. Their overall risk of bias was serious, primarily driven by confounding by indication—women likely received ART due to fertility issue—and incomplete adjustment for known and unknown confounders. Moreover some studies might have underestimated the total ES by adjusting for factors like pre-eclampsia and plurality, which are potential mediators rather than confounders.[7,14,15,19,20] Of note, Farland *et al.*[20] performed a sensitivity analysis that excluded an effect modification by plurality on their results.

A further constraint of our study was the inability to consider death a competing risk event, as death may preclude the occurrence of the event of interest, introducing potential competing risk bias. Only Wei *et al.*[22] accounted for death as a competing risk. To mitigate this issue, we included death in the MACE definition whenever it was reported. Additionally, Westerlund *et al.* observed identical mortality rates (0.5% vs. 0.5%) between groups, and the overall low and comparable mortality rates between cases and controls suggest this bias is likely minimal.[16]

There was significant heterogeneity in the definitions of MACE, time horizons, and effect measures (HR, RR, or OR) used across studies (see Supplementary data online, *Table S2*). While we pooled these measures as they are generally comparable when the incidence proportion or risk is below 1%, we acknowledge they represent different measures of association. To address the variability in MACE definitions, we analysed the individual components of the endpoint separately, providing risk estimates for coronary heart disease and heart failure for the first time. To address heterogeneity in time horizons, we performed the cumulative and subgroup analyses.

We also acknowledge that multiple hypothesis testing in this study increases the potential for type I errors. After applying corrections for multiple comparisons—such as the Bonferroni adjustment—the association between ART and heart failure risk becomes only borderline significant, emphasizing the need for further research to clarify this ambiguous finding.

We attempted to increase the coverage and granularity of our data by reaching out to the corresponding authors of each study. However, we were unable to obtain individual-patient data or additional information on baseline characteristics and outcomes. We suggest that future efforts to collect this data are warranted to address the limitations of our study and provide more robust conclusions.

Conclusions

Assisted reproductive technology does not appear to be significantly associated with an increased long-term risk of cardiovascular diseases. While these findings suggest long-term cardiovascular safety and may reassure the growing population relying on ART for conception, further research is warranted to confirm these results and to investigate potential short-term cardiovascular risks associated with specific ART techniques.

Supplementary data

Supplementary data are available at *European Heart Journal* online.

Declarations

Disclosure of Interest

All authors declare no disclosure of interest for this contribution.

Data Availability

All data are study-level and included in the main paper. No patient-level or additional data were generated or analysed for or in support of this paper.

Funding

All authors declare no funding for this contribution.

Ethical Approval

Ethical Approval was not required.

Pre-registered Clinical Trial Number

This study is registered with PROSPERO (CRD42024505605).

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