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Review article

# Particulate matter ($PM_{2.5}$, $PM_{10}$) exposure and assisted reproductive technology outcomes in fresh cycles: a systematic review and meta-analysis

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## HIGHLIGHTS

- Assessed the impact of $PM_{2.5}$ and $PM_{10}$ on ART success rate in fresh embryo transfer.
- Based on 14 studies with 333,438 ART cycles across four specific exposure timeframes.
- No association between PM and biochemical, clinical pregnancy, or live birth.
- Moderate heterogeneity in outcomes and exposure periods.
- Need for standardized methodologies to evaluate pollution risks in ART.

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## ABSTRACT

Several studies have assessed the relationship between exposure to particulate matter with aerodynamic diameters ≤2.5 μm ($PM_{2.5}$) and ≤10 μm ($PM_{10}$) and assisted reproduction technology (ART) success rates, with controversial findings. This review aimed to consolidate the current evidence from fresh ART cycles and explore sources of heterogeneity across studies. The outcomes of interest were biochemical and clinical pregnancy, and live birth. Four exposure timeframes were considered: T0 (within 90 days before starting the stimulation protocol), T1 (from the first day of stimulation protocol to oocyte retrieval), T2 (from oocyte retrieval to embryo transfer), and T3 (from embryo transfer to pregnancy).

Database searches were conducted on PubMed/Medline and Embase up to April 2025, using a combination of MeSH/Emtree and generic terms relating to ART patients and air pollution exposure. Fourteen studies, involving 333,438 cycles, were included in the meta-analysis. The studies were conducted between 2010 and 2024 primarily in China (10/14), while 3 were from the USA and one from Korea. We estimated pooled relative risks (RRs) and the corresponding 95% confidence intervals (CIs) for a 10 $\mu g/m^3$ increase in $PM_{2.5}$ and $PM_{10}$ for biochemical pregnancy, clinical pregnancy, and live births, using random-effects meta-analytic models.

The pooled RRs for 10 $\mu g/m^3$ increment in $PM_{2.5}$ and $PM_{10}$ at T0 were respectively 0.97 (95%CI: 0.91–1.04) and 0.98 (95%CI: 0.95–1.02) for biochemical pregnancy; for clinical pregnancy they were respectively 0.98 (95% CI: 0.96–1.01) and 0.99 (95%CI: 0.98–1.00). All other findings were close to unity. Substantial heterogeneity was observed across studies for selected outcomes and exposure periods for both pollutants.

This systematic review found no significant association between $PM_{2.5}$ and $PM_{10}$ exposure and ART outcomes after fresh embryo transfer for any of the four exposure windows.

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## 1. Introduction

Air pollution has been recognized by the World Health Organization as one of the five major risk factors for non-communicable disease, alongside with unhealthy diet, smoking, harmful use of alcohol, and physical inactivity (Fuller et al., 2018). A substantial component of public health has targeted it as one of the most successful strategies for disease and injury prevention (GBD, 2020; UN Environment Programme, 2019). While on one hand the possible influence of air pollutants on the risk of cancer, cardiovascular, and respiratory disease has been extensively recognized (Cierpial-Wolan et al., 2023; Kornfield et al., 2024; Krittanawong et al., 2023; Maio et al., 2023), on the other hand high interest has recently been addressed to their potential impact on human reproduction and offspring outcomes (Conforti et al., 2018; Olutola and Phoobane, 2023; Soesanti et al., 2023; Stieb et al., 2016). A particularly worrisome consequence could be in fact the reproductive toxicity. Considering only natural conceptions, a recent review has suggested a longer time to pregnancy due to outdoor air pollutants exposure, although results are still controversial (Siegel et al., 2023). However, the study of the determinants of natural fecundability is challenging and subject to biases ranging from the time lag between exposure and outcome to the inclusion of couples with different fecundability at baseline. Further, the reproductive chances of a couple are influenced by both male and female factors, which may be affected by pollution in different ways and with different exposure windows. For example, acute exposure may lower semen quality (Zhao et al., 2022) while chronic one could increase the risk of polycystic ovarian syndrome in women (Merkin et al., 2016).

The evaluation of the impact of air pollutants on assisted reproductive technology (ART) outcomes may theoretically and, at least partially, overcome these methodological biases (Canipari et al., 2020) for various reasons: i) women undergoing ART procedures are infertile and, as such, possibly more vulnerable to environmental pollutants; ii) the reproductive event may be assessed across the different underlying processes since ART procedures allow to evaluate different steps and timings. Overall, the ART model of fertility can provide valuable information, even if inevitably incomplete (ART differs from natural conception in several aspects).

Particulate matter (PM), including inhalable particles (aerodynamic-mass median diameter, <10 μm [$PM_{10}$]) and fine particles (<2.5 μm [$PM_{2.5}$]) was selected as exposure metric because it is widely measured, data are readily available, and there are well-established links between it and adverse health outcomes. These PM fractions are the most studied and monitored, providing a solid basis for analysis (Chen and Hoek, 2020). PM is a heterogeneous mixture of solid and liquid particles suspended in the air which vary in size and chemical composition over space and time. While $PM_{2.5}$ usually originates primarily from combustion sources, $PM_{10}$ derives largely from crustal material, sea salt, and biological material (WHO, n.d.). The concern about $PM_{2.5}$ and $PM_{10}$ stems from the evidence supporting their causative role in increased mortality from all causes, cardiovascular disease, respiratory disease, and lung cancer (Chen and Hoek, 2020).

On this basis, the purpose of this systematic review and meta-analysis is to synthesize the available evidence on the effect of exposure to outdoor air pollution with $PM_{2.5}$ and $PM_{10}$ on fertility by focusing on biochemical pregnancy, clinical pregnancy and live birth rates in women undergoing fresh ART cycles.

## 2. Materials and methods

The current review follows the PRISMA guidelines for reporting systematic reviews and meta-analysis (Page et al., 2021). The protocol was registered at the International Prospective Register of Systematic Reviews (PROSPERO, registered ID: CRD42022342530).

### 2.1. Information sources, search, and eligibility criteria

We applied the following eligibility (inclusion and exclusion) criteria structured by PECOS items.

Population: female population undergoing ART procedures, meaning ovarian stimulation, oocyte retrieval, and embryo transfer (we considered only fresh embryo transfers). No restrictions on ages, type of ART, or geographical areas was applied.

Exposure: ambient air $PM_{2.5}$ and $PM_{10}$ exposure, assessed at least in one of the following periods: T0 - within 90 days before starting stimulation protocol; T1 - from the first day of stimulation protocol to oocyte retrieval; T2 - from oocyte retrieval to embryo transfer; and T3 - from embryo transfer to pregnancy diagnosis, defined by the β-hCG value at blood sample or positive ultrasound (Fig. 1). Studies covering exposure periods differing from those defined above were reported and their inclusion was evaluated on a case-by-case basis.

Comparator: women undergoing ART procedures from the same cohort of the participants, not exposed/exposed to lower levels of the same factors than the more highly exposed ones (i.e., a comparison across a range of exposure).

Outcomes: biochemical pregnancy (β-hCG positive at the blood sample), clinical pregnancy (showing at least one fetus with a discernible heartbeat at ultrasound), and live birth (the birth of at least one liveborn infant). We selected studies reporting an estimate of the relative risks (RRs) - including odds ratios and hazard ratios - of the selected outcomes with corresponding 95% confidence intervals (CIs), or data allowing their calculation.

Study: we included original studies with a cohort design. Relevant reviews and systematic reviews were not included in the current systematic review but used to scan for references. Only publications in English were considered. We identified relevant literature from PubMed/Medline (http://www.ncbi.nlm.nih.gov/pubmed) and Embase (http://apps./online-tools/embase) databases, with no limitation on publication date, until April 2025. We developed a search string by using a combination of MeSH/Emtree and generic terms regarding ART patients as population and air pollution as exposure. The complete search string is given in Table S1. We also hand searched the reference list of 1) included studies, 2) pertinent reviews identified by the search. Two review authors (LLP, VS) independently selected the studies. A third author (FP) was involved in case of discrepancy. The procedure of study selection is reported in Fig. 2.

### 2.2. Data extraction and risk of bias assessment

Three authors (LLP, ILV, and VS) extracted the data from all the included studies. We collected details on study characteristics (i.e., country, study design, population characteristics, and size), type of outcome and exposure and related data source, period of exposure, type of analysis, adjustments, and effect estimates. Three authors (LLP, ILV, and VS) classified each study for period of exposure analysed. Two authors (LLP and GE) independently assessed the risk of bias according to the assessment instrument for epidemiologic studies on air quality and health proposed by the WHO Global Air Quality Guidelines Working Group on Risk of Bias Assessment (WHO Regional Office for Europe, 2020), which evaluates 6 different domains: confounding, selection bias, exposure assessment, outcome measurement, missing data, and selective reporting.

### 2.3. Statistical analysis

If three or more studies were available for the same pollutant, outcome, and exposure time period, a meta-analysis was performed. We used RR as the measure of associations between the three outcomes considered and a 10 $\mu g/m^3$ increase in particulate air pollution ($PM_{2.5}$ and $PM_{10}$). We assumed a linear relationship between exposure and outcomes, which is consistent with the approach used in most of the

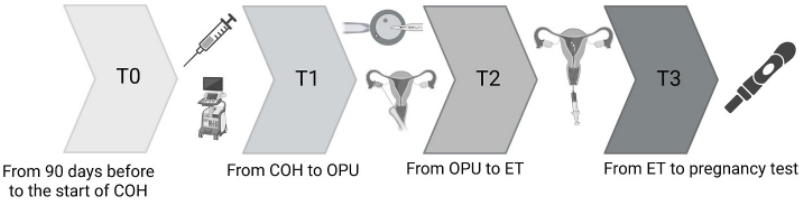


**Fig. 1.** Timeline of exposure periods of an in vitro fertilization cycle (IVF) from 90 days before starting protocol to the serum β-hCG test/ultrasound to assess the gestational sac. Abbreviations: COH, controlled ovarian hyperstimulation; ET, embryo transfer; OPU, oocyte pick up.

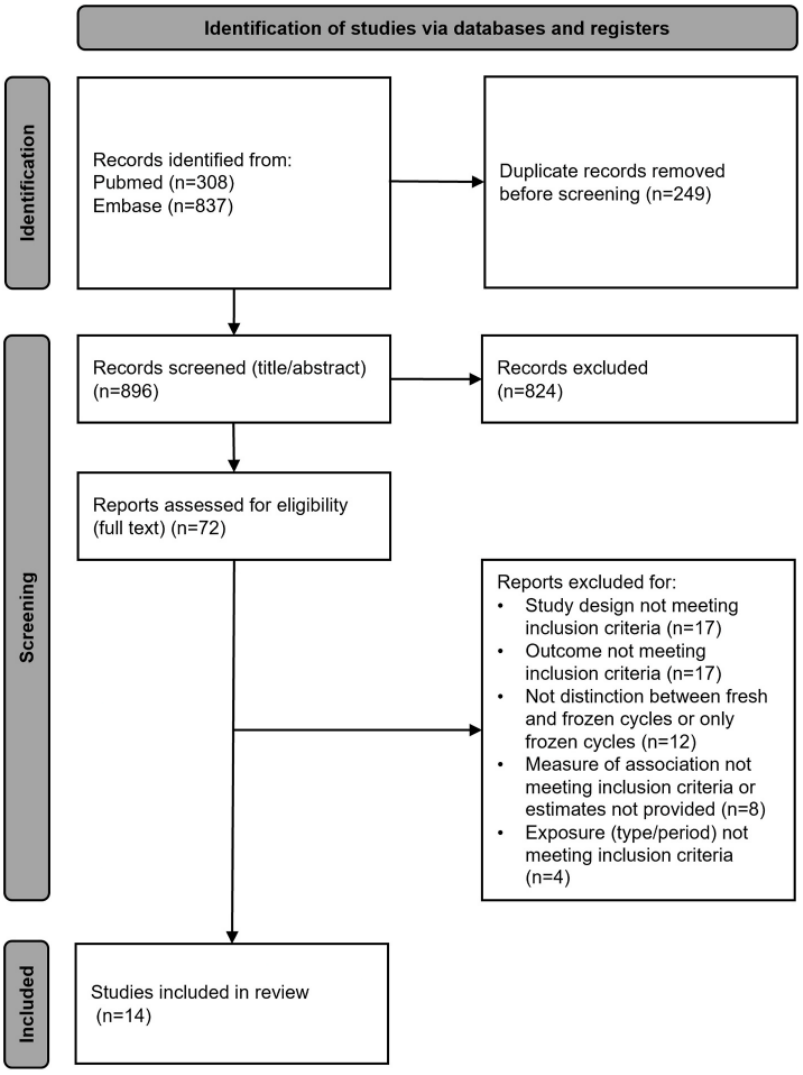


**Fig. 2.** Flowchart for the study selection process.

included studies, as well as in the broader air pollution epidemiology literature, where generalized linear models are typically used to estimate the effects of air pollution on health outcomes. This assumption is commonly made in environmental epidemiology meta-analyses (Conforti et al., 2018; Hoek et al., 2013; Shah et al., 2013).

When RR estimates were provided for increments other than 10 μg/m$^3$ (e.g., per interquartile range increase), we converted the estimates. Slope and standard error per 1 μg/m$^3$ were computed, multiplied by 10, and then exponentiated, using the standard formulas. When the RR estimates were reported for a categorical exposure of particulate air pollution, we derived estimates per 10 μg/m$^3$, by determining the trend using variance-weighted least-squares linear regression. If an article

reported two or more estimates for subsets of the study population separately (i.e., age groups, geographical areas, and number of embryos), we considered single group-specific estimates. We estimated pooled RRs for 10 μg/m$^3$ increase in particulate air pollution for biochemical pregnancy, clinical pregnancy, and live births, using random-effects meta-analytic models. These estimates were provided separately for $PM_{2.5}$ and $PM_{10}$ as well as for each period considered. We also considered Cochran's $\chi^2$ test and $I^2$ statistic to evaluate heterogeneity and inconsistency across studies. To assess whether the results could have been significantly influenced by a single study, an influence analysis was performed with one study removed at a time. To evaluate publication bias, we examined the funnel plots (Sterne and Egger, 2001) and used Egger's test for funnel plot asymmetry (Egger et al., 1997), for each time interval already described. Trim and fill analysis was also conducted to obtain an alternative adjusted pooled estimate (Duval and Tweedie, 2000). Finally, as a sensitivity analysis, we repeated the analysis including only studies that adjusted for socioeconomic status (using education level as a proxy), assuming that this was the main confounding factor. This was not possible for all time periods and outcomes, as in some cases excluding studies that did not adjust for socioeconomic status resulted in fewer than three studies being available. All statistical analyses were performed using the package *meta* of R software version 4.1.2 (R Development Core Team, 2021) and STATA software version 17, in particular the command "*vwls*".

## 3. Results

### 3.1. Literature retrieval and systematic review

The initial search returned 1145 records from two databases with no additional records from the bibliographic lists, 249 records were removed as duplicates and 824 as irrelevant (Fig. 2). Of 72 studies that underwent in-depth full-text review, 14 studies met the inclusion criteria (Boulet et al., 2019; Choe et al., 2018; Dai et al., 2021; Jin et al., 2022; Legro et al., 2010; Li et al., 2020; Liu et al., 2022, 2024; Qiu et al., 2019; Quraishi et al., 2019; Wang et al., 2023a; Wu et al., 2021; Zeng et al., 2020; Zhang et al., 2022). The main characteristics of the eligible studies are summarized in Table 1, including country, study design, population, exposure (type and timeframes), and outcomes (more detailed information was available in Supplemental Table S2). While the majority of papers were retrospective (Boulet et al., 2019; Choe et al., 2018; Dai et al., 2021; Jin et al., 2022; Li et al., 2020; Liu et al., 2022, 2024; Qiu et al., 2019; Quraishi et al., 2019; Wu et al., 2021; Zeng et al., 2020; Zhang et al., 2022), two had a prospective design (Legro et al., 2010; Wang et al., 2023a). The studies were mainly conducted in China (10 studies), while others in the USA (3 studies), and one in Korea, published between 2010 and 2024. The sample sizes of the studies ranged from 1455 to 12,665 women. A wide range of concentrations across air pollutants was included in the papers; for example, $PM_{2.5}$ ranged from 1.7 to 150 μg/m$^3$ and $PM_{10}$ from 1.00 to 225 μg/m$^3$. The methods for exposure assessment were mainly based on the estimate of individual exposure at the city/countrywide level based on the real-time monitoring data from national or regional surveillance sites.

### 3.2. Risk of bias

A summary of the risk of bias assessment of the included studies is provided in Fig. S1. No issue was found concerning outcome assessment and selective reporting. The most severe risk of bias was in the area of confounding, with 13 studies (93%) classified at high risk, missing at least one of the critical potential confounding factors, including BMI, socio-economic status, type/duration of infertility, or seasonality. One study (7%) was classified at "moderate risk" for selection bias because the authors were not able to assess correlations among cycles of the women who contributed multiple cycles (Boulet et al., 2019). As for exposure assessment, only one study (7%) was rated "moderate risk"

**Table 1**
Summary description of studies characteristics.

| | | Nr of studies | References |
|---|---|---|---|
| *Country* | China | 10 | (Dai et al., 2021; Jin et al., 2022; Li et al., 2020; Liu et al., 2022, 2024; Qiu et al., 2019; Wang et al., 2023a; Wu et al., 2021; Zeng et al., 2020; Zhang et al., 2022) |
| | USA | 3 | (Boulet et al., 2019; Legro et al., 2010; Quraishi et al., 2019) |
| | Korea | 1 | Choe et al. (2018) |
| *Study design* | Retrospective cohorts | 12 | (Boulet et al., 2019; Choe et al., 2018; Dai et al., 2021; Jin et al., 2022; Li et al., 2020; Liu et al., 2022, 2024; Qiu et al., 2019; Quraishi et al., 2019; Wu et al., 2021; Zeng et al., 2020; Zhang et al., 2022) |
| | Prospective cohorts | 2 | (Legro et al., 2010; Wang et al., 2023a) |
| *Population* | Cycles | 2 | (Boulet et al., 2019; Liu et al., 2022) |
| | Women | 8 | (Dai et al., 2021; Jin et al., 2022; Legro et al., 2010; Liu et al., 2024; Qiu et al., 2019; Quraishi et al., 2019; Wang et al., 2023a; Zeng et al., 2020) |
| | Cycles/women | 4 | (Choe et al., 2018; Li et al., 2020; Wu et al., 2021; Zhang et al., 2022) |
| *Exposure* | $PM_{2.5}$ | 12 | (Boulet et al., 2019; Dai et al., 2021; Jin et al., 2022; Legro et al., 2010; Li et al., 2020; Liu et al., 2024; Qiu et al., 2019; Quraishi et al., 2019; Wang et al., 2023a; Wu et al., 2021; Zeng et al., 2020; Zhang et al., 2022) |
| | $PM_{10}$ | 12 | (Choe et al., 2018; Dai et al., 2021; Jin et al., 2022; Legro et al., 2010; Li et al., 2020; Liu et al., 2022, 2024; Qiu et al., 2019; Quraishi et al., 2019; Wu et al., 2021; Zeng et al., 2020; Zhang et al., 2022) |
| *Exposure time* | T0 | 6 | (Dai et al., 2021; Jin et al., 2022; Li et al., 2020; Qiu et al., 2019; Quraishi et al., 2019; Zeng et al., 2020) |
| | T1 | 11 | (Boulet et al., 2019; Choe et al., 2018; Dai et al., 2021; Jin et al., 2022; Legro et al., 2010; Li et al., 2020; Qiu et al., 2019; Wang et al., 2023a; Wu et al., 2021; Zeng et al., 2020; Zhang et al., 2022) |
| | T2 | 10 | (Boulet et al., 2019; Choe et al., 2018; Jin et al., 2022; Legro et al., 2010; Li et al., 2020; Liu et al., 2024; Qiu et al., 2019; Wang et al., 2023a; Wu et al., 2021; Zeng et al., 2020) |
| | T3 | 11 | (Boulet et al., 2019; Choe et al., 2018; Jin et al., 2022; Legro et al., 2010; Li et al., 2020; Liu et al., 2022, 2024; Qiu et al., 2019; Wang et al., 2023a; Wu et al., 2021; Zeng et al., 2020) |
| *Outcome* | Biochemical pregnancy | 3 | (Legro et al., 2010; Zeng et al., 2020; Zhang et al., 2022) |
| | Clinical pregnancy | 12 | (Choe et al., 2018; Dai et al., 2021; Jin et al., 2022; Legro et al., 2010; Li et al., 2020; Liu et al., 2024; Qiu et al., 2019; Quraishi et al., 2019; Wang et al., 2023a; Wu et al., 2021; Zeng et al., 2020; Zhang et al., 2022) |
| | Live birth | 8 | (Boulet et al., 2019; Dai et al., 2021; Legro et al., 2010; Liu et al., 2022; Quraishi et al., 2019; Wang et al., 2023a; Wu et al., 2021; Zhang et al., 2022) |

because misclassification of exposure due to inaccurate localization was not excluded (Quraishi et al., 2019). Finally, 5 studies (36%) were classified as "moderate risk" for missing data domain (Boulet et al., 2019; Liu et al., 2022; Wang et al., 2023b; Wu et al., 2021; Zhang et al., 2022).

### 3.3. Meta-analysis results

A total of 14 studies, involving 333,438 ART cycles, were included in the meta-analysis. The study-specific and pooled RRs of outcomes of interest (i.e., biochemical pregnancy, clinical pregnancy, and live birth) are reported in Figs. 3–6 according to the period of exposure.

Regarding period T0, the meta-analysis was not performed for live birth outcome because only two studies were available. The pooled RRs for 10 μg/m$^3$ increment in $PM_{2.5}$ and $PM_{10}$ during T0 were respectively 0.97 (95%CI: 0.91–1.04) and 0.98 (95%CI: 0.95–1.02) for biochemical pregnancy; for clinical pregnancy they were respectively 0.98 (95%CI: 0.96–1.01) and 0.99 (95%CI: 0.98–1.00) (Fig. 3).

The RRs for each 10 μg/m$^3$ increment in $PM_{2.5}$ or $PM_{10}$ exposure during T1 for biochemical pregnancy, clinical pregnancy, or live births were 1.00 (95%CI: 1.00–1.00), 1.00 (95%CI: 0.99–1.00), and 1.00 (95% CI: 0.99–1.01) respectively for $PM_{2.5}$ and 1.00 (95%CI: 0.98–1.01), 1.00 (95%CI: 0.99–1.01), and 1.00 (95%CI: 0.99–1.01) for $PM_{10}$ (Fig. 4).

Fig. 5 shows pooled estimates for exposure measured from oocyte collection to embryo transfer (T2), with RRs close to unity for both pollutants and all outcomes. The RRs for biochemical pregnancy were respectively 0.99 (95%CI: 0.98–1.01) and 1.00 (95%CI: 0.98–1.01) for $PM_{2.5}$ and $PM_{10}$; for clinical pregnancy, they were respectively 1.00 (95%CI: 0.99–1.00) and 1.00 (95%CI: 0.99–1.01), while for live birth, they were respectively 1.00 (95%CI: 0.99–1.01) and 1.00 (95%CI: 0.99–1.00).

With regard to period T3, the pooled RRs for 10 μg/m$^3$ increment in $PM_{2.5}$ and $PM_{10}$ were respectively 0.99 (95%CI: 0.98–1.01) and 0.99 (95%CI: 0.98–1.01) for biochemical pregnancy, 0.99 (95%CI: 0.98–1.01) and 1.00 (95%CI: 0.99–1.00) for clinical pregnancy, and 1.00 (95%CI: 1.00–1.00) and 1.00 (95%CI: 0.99–1.01) for live birth (Fig. 6).

Even if substantial heterogeneity emerged across studies for selected outcomes and period of exposure for both $PM_{2.5}$ and $PM_{10}$ (Figs. 3–6), when influence analysis was performed, minimal variability among the included studies was observed.

No publication bias was detected (Fig. S2–S5). However, as statistical power was limited when the number of studies was less than 10, undetected publication bias may still be present. Nevertheless, the trim-and-fill corrected estimates were similar to the original estimates for each exposure time and each outcome, approaching unity (Table S3).

Restricting analysis only to studies adjusting for socioeconomic status led to similar results, with the exception of a weak inverse association between $PM_{10}$ exposure at T0 and clinical pregnancy (RR = 0.99, 95%CI: 0.98–0.99) (Table S4).

## 4. Discussion

### 4.1. Main findings

The current systematic review found no significant association between exposure to particulate matters ($PM_{2.5}$ and $PM_{10}$) and ART outcomes involving fresh embryo transfers, across any of the four examined time windows of exposure.

The effect of air pollution on reproduction is controversial. Negative impacts have been reported for sperm DNA fragmentation, sperm aneuploidy, sperm concentration, and motility (Henry et al., 2021; Wieczorek et al., 2024). Studies assessing female fertility showed that exposure to PM can lead to decreased ovarian reserve and lower Anti-Müllerian hormone levels (Wieczorek et al., 2024; Wu et al., 2022). PM may also directly affect the developing embryo by triggering immune or hypoxia-related responses after crossing the placental barrier (Glencross et al., 2020), damaging embryonic DNA, and impairing placental blood perfusion through alterations in haematological dynamics, such as increased blood viscosity (Liu et al., 2016), levels, and changes in blood pressure (Westberg et al., 2019). In this context, evaluating ART outcomes is theoretically helpful since it allows precisely monitoring some crucial steps of the human reproductive process. As a matter of fact, any potential link between exposure to air pollution and the final endpoint of ART procedures, represented by the pregnancy rate, is difficult to assess for several reasons.

An important issue is given by the use of air pollution levels from the municipality at patients' residential addresses for most of the analyses

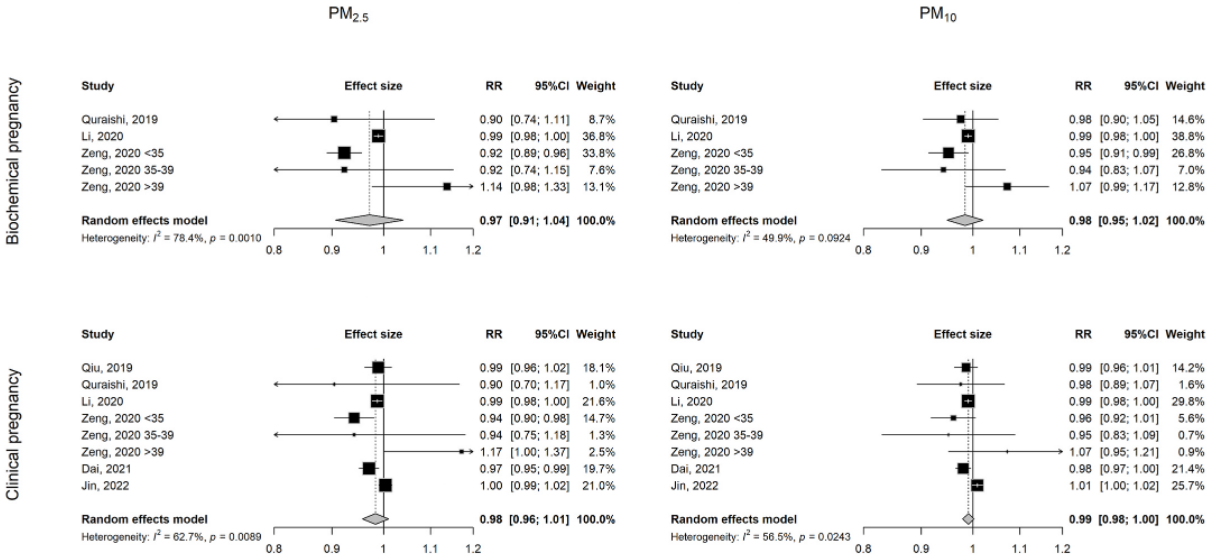


**Fig. 3.** Study-specific and pooled relative risks (RRs) of biochemical and clinical pregnancy, with corresponding 95% confidence intervals (CIs), per 10 μg/m$^3$ increase in $PM_{2.5}$ and $PM_{10}$ for exposure measured before starting stimulation protocol (T0).

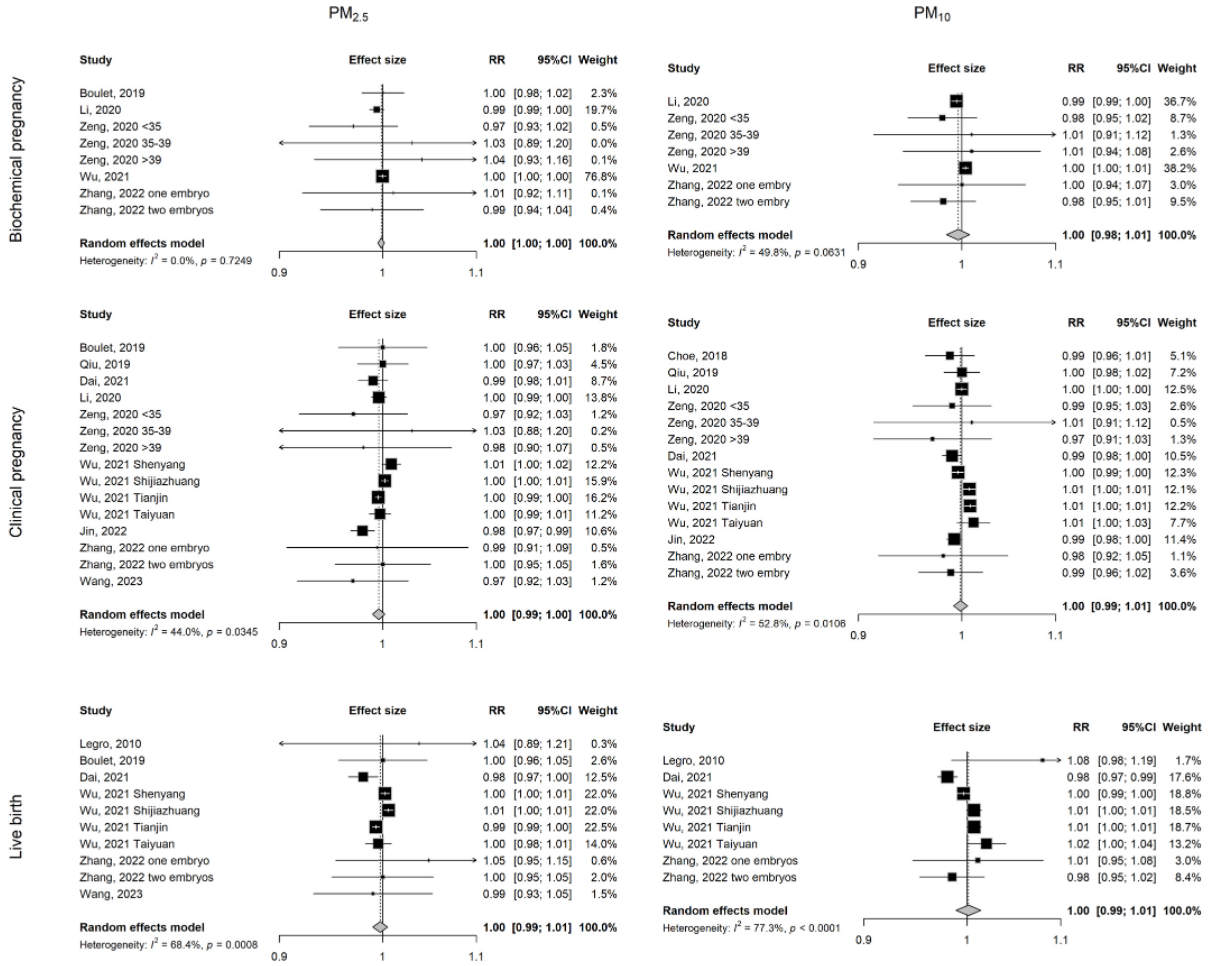


**Fig. 4.** Study-specific and pooled relative risks (RRs) of biochemical, clinical pregnancy, and live birth, with corresponding 95% confidence intervals (CIs), per 10 μg/m$^3$ increase in $PM_{2.5}$ and $PM_{10}$ for exposure measured from the first day of stimulation protocol to oocyte retrieval (T1).

performed (Boulet et al., 2019; Choe et al., 2018; Jin et al., 2022; Legro et al., 2010; Li et al., 2020; Liu et al., 2022, 2024; Qiu et al., 2019; Quraishi et al., 2019; Wang et al., 2023a; Wu et al., 2021; Zeng et al., 2020; Zhang et al., 2022). Indeed, the air quality of the patients' workplace or of the ART laboratory could be equally or even more informative. Evaluating pollution at the residential location does not reflect exposure occurring at the workplace and during transport, which could be major locations for personal exposure (Iodice et al., 2021). Regarding the laboratory, a recent study evaluated the impact of unhealthy air quality on ART outcomes from the 6 weeks preceding the exposure through a 10-day exposure period and classified the cohorts on the basis of whether subjects experienced patient and/or laboratory exposure. Patients' exposure was defined as at least 4 days of ovarian stimulation overlapping with the exposure, and clinic exposure was defined as at least 2 days of ART treatment and embryo culture overlapping with the exposure. Results obtained showed no significant differences in ART treatment outcomes between exposed and unexposed cohorts, but also demonstrated a decreased blastocyst yield in the laboratory exposure cohort (Kornfield et al., 2024). Air in an ART laboratory is a critical issue (Sciorio et al., 2021) and any investigation addressing patients' exposure to pollutants should include this aspect. Two studies included in the current meta-analysis (Dai et al., 2021; Jin et al., 2022) considered the PM concentration of the city where the clinic was placed. In addition, two other studies considered air pollution measurements from the clinic location only for the period between oocyte retrieval and embryo transfer, when the embryo is cultured in the laboratory (Boulet et al., 2019; Liu et al., 2022).

The location of air pollution monitoring is a relevant factor when assessing its potential impact on ART outcomes, as it relates to different underlying mechanisms. Air pollution measured at a patient's workplace or residence more likely reflects the chronic exposure that may eventually impact on the individual reproductive function. Indeed, hormonal alterations, oxidative stress induction, DNA damage, and epigenetic modifications have all been proposed as mechanisms through which air pollution may impair gametogenesis, potentially leading to a subfertile or infertile phenotype (Carré et al., 2017) or compromise obstetrical outcomes (Huang et al., 2023). In contrast, air quality within the in vitro fertilization (IVF) lab environment is more relevant to the in vitro phase of the fertilization and then the development of the embryo, justifying the strict environmental control as a fundamental standard in ART laboratory practice (De los et al., 2016). Therefore, distinguishing between sources and sites of exposure is essential when interpreting associations between PM and specific ART endpoints.

Measures of air quality in residential environments and IVF labs are

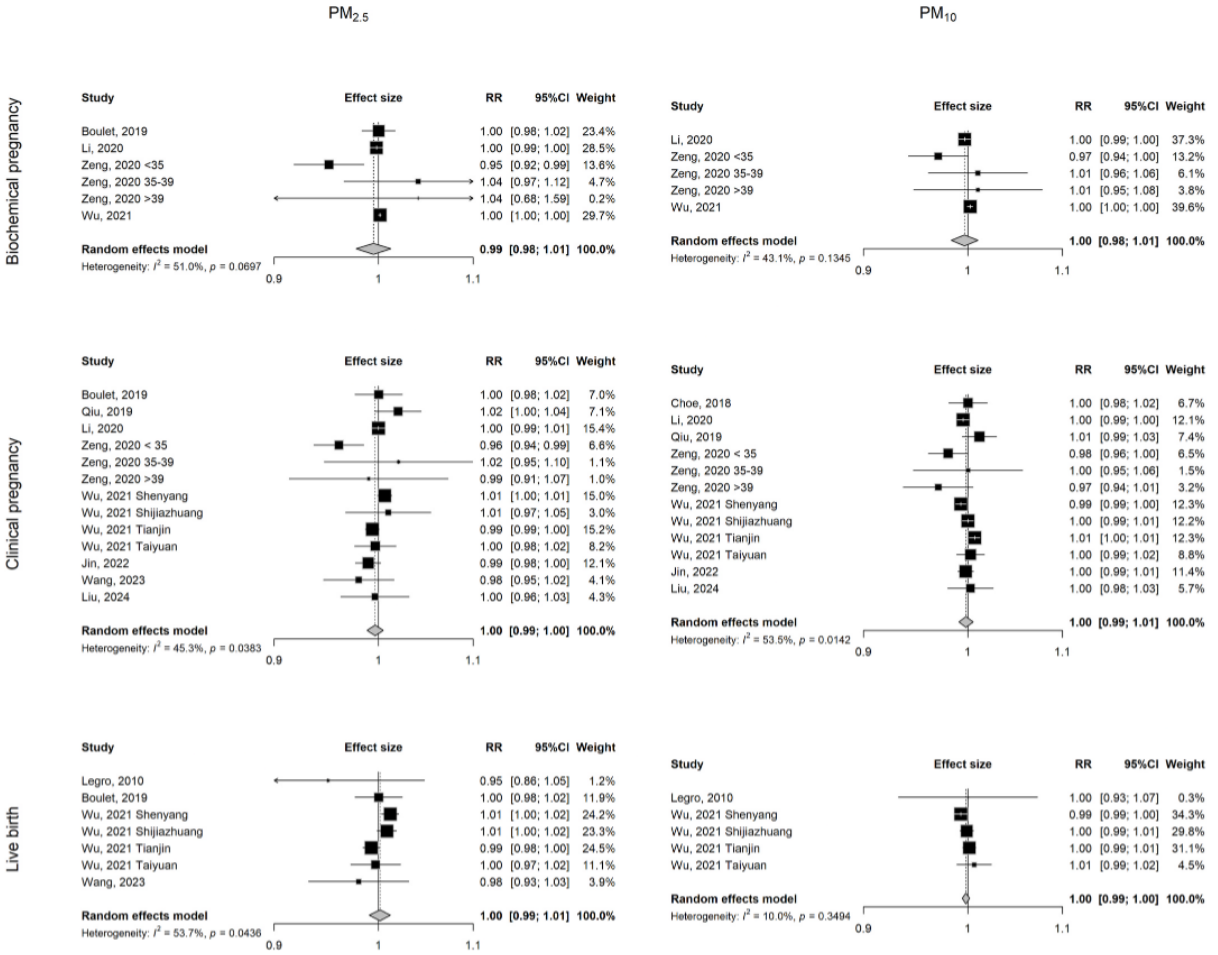


**Fig. 5.** Study-specific and pooled relative risks (RRs) of biochemical, clinical pregnancy, and live birth, with corresponding 95% confidence intervals (CIs), per 10 μg/m$^3$ increase in $PM_{2.5}$ and $PM_{10}$ for exposure measured from oocyte retrieval to embryo transfer (T2).

methodologically different. In fact, while chronic exposure is typically estimated based on air quality monitoring stations near to the patient's residence, providing only an approximative proxy of individual exposure, IVF labs follow stringent protocols not only to minimize the air contamination of high-efficiency particulate air and volatile organic compounds, but also to monitor continuously the air to ensure a stable and contaminant-free room for gamete or embryo manipulation (De los et al., 2016).

Another important issue associated with this kind of analyses refers to the choice of the different time windows in which air pollutants may affect the successful pregnancy of ART patients. ART treatment can be subdivided into several distinct periods for a discrete analysis to reveal potentially vulnerable window periods. As previously mentioned, the idea to study the relationship between air pollution levels and treatment outcomes at discrete treatment periods should allow to delineate specific periods affecting pregnancy outcomes to provide recommendations for women on avoiding heavily polluted days (Liu et al., 2022). Although there is still no standardised consensus between studies, aligning time windows with key time nodes during the ART process may increase comparability and improve interpretation of the effects of air pollution on ART outcomes. Specifically, we identified time nodes based on oocyte development and the clinical course of ART: ovarian stimulation, oocyte retrieval, and embryo development. However, the need to distinguish acute, subacute or long-term exposure has led to the establishment of poorly comparable time-windows among various reports (Gonzalez-Comadran et al., 2021).

Finally, investigations on this topic are characterized by differences in exposure assessment methods, study design, study area, pollutant chemical components, adjustment covariates, study population, type of stimulation regimens used, duration of infertility and ART procedure itself (Liu et al., 2023). This can explain the substantial heterogeneity detected among the studies. Moreover, results obtained are poorly generalizable if we consider that among the 14 included reports, nine could be geographically located in China and three in the USA while the rest of the world was not represented.

In line with the possible presence of several variables interfering with the outcome assessment among the available studies due to the above-mentioned factors, controversial findings were derived from the present study and a previous meta-analysis on the same topic (Liu et al., 2023). Evaluating four time periods of exposure, we could not demonstrate that the environmental exposures to $PM_{2.5}$ or $PM_{10}$ had any impact on the success rates of ART procedures. In contrast, the meta-analysis of Liu et al. (2023), investigating the effects of air pollutants during seven different time windows, found that exposure to $PM_{2.5}$ or $PM_{10}$ in the period beginning from 85 days before oocyte retrieval to the beginning of gonadotropin administration was linked to

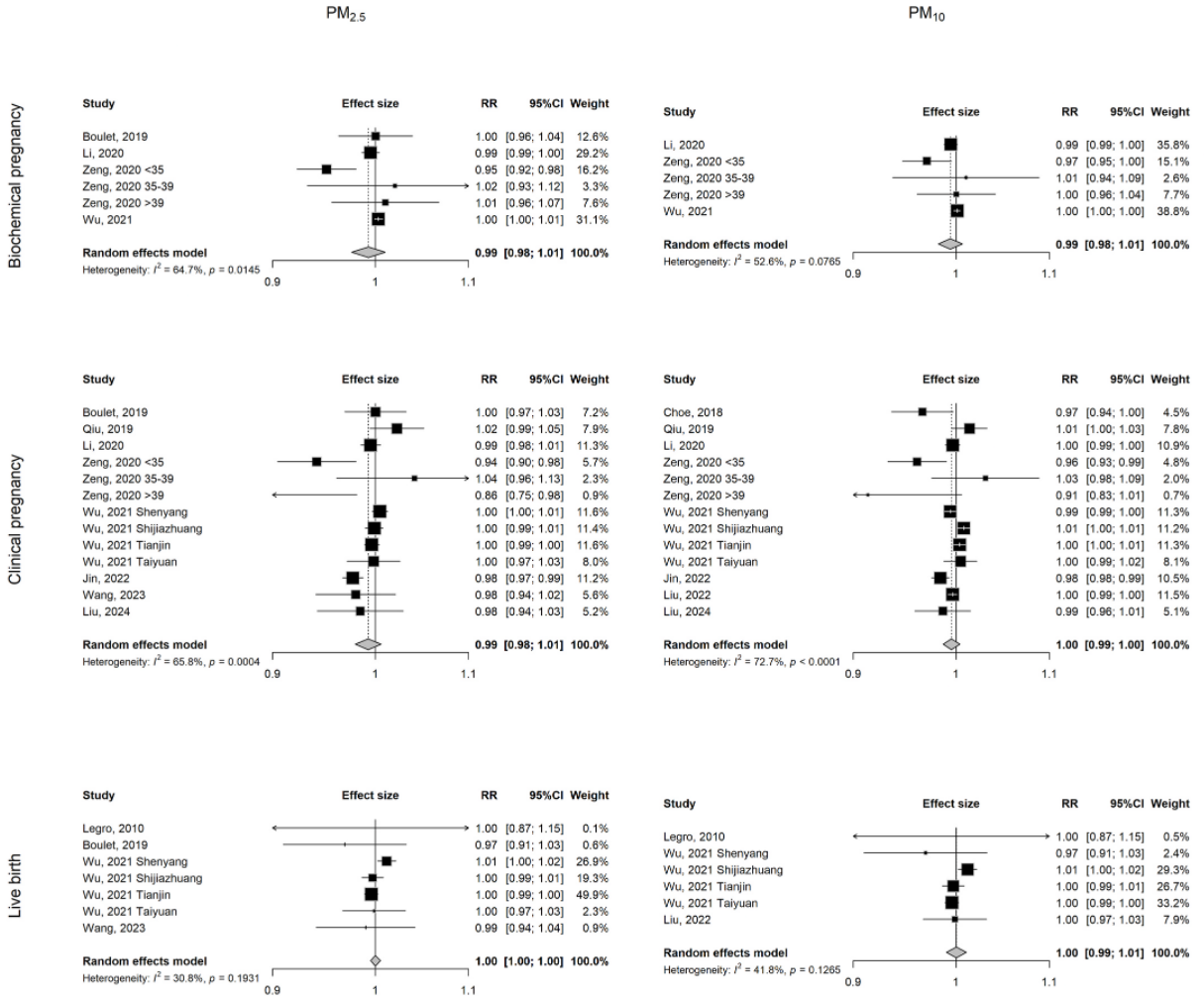


**Fig. 6.** Study-specific and pooled relative risks (RRs) of biochemical, clinical pregnancy, and live birth, with corresponding 95% confidence intervals (CIs), per 10 μg/m$^3$ increase in $PM_{2.5}$ and $PM_{10}$ for exposure measured from embryo transfer to pregnancy (T3).

lower likelihood of biochemical pregnancy and live birth (Liu et al., 2023). The two aggregate analyses differ in the choice of ART timeframes of pollutant exposure. For instance, period 1 of Liu et al. corresponded to 85 days before oocyte retrieval to the beginning of gonadotropin administration, while in our meta-analysis we considered the concentration between the start of stimulation protocol and the oocyte retrieval procedure (Liu et al., 2023). However, the most striking difference refers to the inclusion of frozen embryo cycles in the study by Liu et al. (2023) which were excluded in our paper. In frozen cycles, the timeframe between ovarian stimulation to gamete fertilization and embryo development is very difficult to assess as potential exposure as it refers to a previous cycle. For this reason, we focused our attention and included only studies addressing the impact of pollutants on fresh ART cycles encompassing the ART process for the entire course.

Finally, from a biologic standpoint, we cannot exclude that the controversy among the studies may be partly explained by the ability of IVF procedures to overcome most of the negative effects of air pollutants on the reproductive process. The accurate selection of motile sperms for intracytoplasmatic sperm injection, the availability of several oocytes to be fertilized following controlled ovarian stimulation, and the in vitro culture of preimplantation embryos in a protected environment may strongly mitigate the hypothesized pollutant-mediated in vivo adverse phenomena.

### 4.2. Strengths

This study presents some strengths. First, our analysis incorporates more datasets compared to other recent meta-analyses (Gholami et al., 2024; Hu et al., 2025; Liu et al., 2023). Even more importantly, we have included only results from fresh embryo transfers. The aggregation of data from both fresh and frozen cycles for the window of exposure of embryo transfer is formally incorrect as the two procedures are completely different in terms of patients' population, pharmacological treatments, embryological parameters, pollutant exposure. The analysis should be corrected for all the possible confounders. Our findings refer only to the effect of pollutants on fresh ART cycles. We cannot exclude an impact of particulate exposure on success rates of embryo frozen cycles. On the other hand, it should be noted that the retrospective analysis of 3698 frozen embryo cycles of women living in Shanghai in relation to daily concentrations of six air pollutants measured at 9 monitoring stations for one month before transfer could not demonstrate any effect of $PM_{2.5}$ or $PM_{10}$ on clinical pregnancy rate (Wan et al., 2022).

### 4.3. Limitations

A limitation of this study is that the analysis focuses on $PM_{2.5}$ and $PM_{10}$, as these are the most widely measured and studied PM fractions. However, other PM types, like ultrafine particles, were not included due to scant availability of data and evidence. Furthermore, the available evidence derived from observational studies, which are prone to several bias. Substantial heterogeneity across studies was observed, hindering generalization of some results, however, the limited number of included studies restricts the feasibility of more extensive subgroup or meta-regression analyses. In addition, the scarcity of studies, especially within each specific exposure window and outcome, may have reduced the statistical power to detect weak associations and may have contributed to the overall nonsignificant findings. Therefore, the observed lack of association should be interpreted with caution. Finally, another limitation is the assumption of linearity in the exposure-response relationship. Although we modelled the association per 10 $\mu g/m^3$ increase in $PM_{2.5}$ and $PM_{10}$, we acknowledge that the true relationship may be non-linear. However, the data reported in the included studies were largely limited to linear effect estimates (e.g., per 1 or 10 $\mu g/m^3$ increase in $PM_{2.5}$ or $PM_{10}$), with very few studies providing results across multiple exposure categories, so we were unable to explore this using flexible models. This suggests that further research is needed, possibly standardizing the reporting to very specific ART procedures in specific windows of exposure.

## 5. Conclusions

By combining results from several original studies, this study could not detect an association between $PM_{2.5}$ and $PM_{10}$ and ART success rates after a fresh embryo transfer. Further evidence considering co-exposures, accounting for vulnerable groups, and investigating other toxic compounds is needed before proposing any possible preventive measures. Standardization of methodology across studies, including exposure windows, regimens of treatment, and treated populations may provide more reliable evidence on the association between air pollutants and ART outcomes.

## CRediT authorship contribution statement

**Letizia Li Piani:** Writing – original draft, Data curation, Conceptualization. **Giovanna Esposito:** Writing – review & editing, Software, Methodology, Investigation, Formal analysis, Data curation. **Eva Negri:** Writing – review & editing, Software, Methodology, Investigation, Formal analysis, Data curation. **Irene La Vecchia:** Writing – review & editing, Data curation. **Vittoria Sterpi:** Writing – review & editing, Data curation. **Claudia Santucci:** Writing – review & editing, Software, Methodology, Investigation, Formal analysis, Data curation. **Rossella Bonzi:** Writing – review & editing, Investigation, Formal analysis, Data curation. **Carlo La Vecchia:** Writing – review & editing, Supervision. **Edgardo Somigliana:** Writing – review & editing, Supervision, Conceptualization. **Paola Viganò:** Writing – original draft, Supervision, Conceptualization. **Fabio Parazzini:** Writing – review & editing, Supervision, Conceptualization.

## Ethical issue

This is a systematic review with meta-analysis and did not involve direct contact with human subjects.

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## Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Edgardo Somigliana reports a relationship with Ferring that includes: funding grants. Edgardo Somigliana reports a relationship with Human Reproduction Open that includes: board membership. Edgardo Somigliana reports a relationship with IBSA Institut Biochimique SA that includes: speaking and lecture fees. Edgardo Somigliana reports a relationship with Gedeon Richter that includes: speaking and lecture fees. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atmosenv.2025.121518.

## Data availability

Systematic review and meta-analysis

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