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Posted Date: 2 July 2025

doi: 10.20944/preprints202507.0028.v1

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Parental Cigarette Smoke Exposure and Its Impact on Offspring Reproductive Health: A Systematic Review of Maternal, Paternal, and Dual-Smoking Effects

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Abstract

The aim of this systematic review was to evaluate the impact of maternal, paternal and dual-parental cigarette smoke exposure on offspring reproductive health. Original human clinical and animal research studies were included; titles and abstracts were manually scanned for relevance to the effect of parental smoking on offspring's reproductive outcomes (Date of search:18/03/2025). This systematic review incorporates 31 studies identified from three databases (PubMed, Web of Science, and Scopus). The results indicate that male offspring exhibit reduced spermatogenic capacity, characterised by decreased testicular size, lower sperm count, and impaired hormonal biosynthesis, with reductions of 30–40% in sperm production. Dual-parental smoking exacerbates these effects, with sperm counts averaging 85 million per ml in human male offspring from dual-smoking households compared to 111 million per ml in single-smoking households. Animal studies provide mechanistic insights, revealing reduced testis weight in nicotine-exposed male rats and increased oxidative stress in offspring. This review highlights the dose-dependent and sex-specific effects of smoking on fertility of the offspring and underscores the need for standardised protocols to enhance the consistency and comparability of future research in both human and animal studies.

Keywords: parental smoking; reproductive health; offspring; maternal exposure; paternal exposure; nicotine effects

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1. Introduction

Parental exposure to tobacco smoke is a significant public health concern, with over 1.1 billion smokers worldwide [1]. According to the World Health Organisation (WHO), tobacco use is responsible for more than 8 million deaths annually, including 1.2 million attributed to second-hand smoke exposure.

Cigarette smoke contains over 7,000 chemical compounds, including nicotine, polycyclic aromatic hydrocarbons (PAHs), and heavy metals, such as lead and cadmium, many of which are toxic to reproductive organs [2,3]. The Developmental Origins of Health and Disease (DOHaD) hypothesis has advanced considerably over the last two decades. It states that fetal adaptations to maternal and paternal environmental conditions during development significantly influence the development and functionality of their offspring's organs and, ultimately, their long-term health. Epidemiological studies indicate that maternal smoking during pregnancy significantly increases the risk of low birth weight and perturbs placental function [4]. Low birth weight is linked to a range of adult-onset conditions [5]. Smoking during pregnancy is now linked to impairments in offspring fertility—giving the potential for there to be impacts across multiple generations, especially if the changes go germline [6]. In-vitro animal studies have also demonstrated that exposure chemical

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compounds derived from cigarettes can damage the developing fetal ovary during the critical period of follicle formation [7].

Paternal smoking also affects the health of offspring, mediated through perturbed sperm quality, DNA fragmentation and epigenetic changes. [8–10]. Studies suggest that fathers who smoke have a 30% higher likelihood of sperm DNA fragmentation, which is linked to poor embryonic development and adverse reproductive outcomes [11].

The combined effects of maternal and paternal smoking further amplify these risks, but these are fewer in number than those examining the effect of just one parent. Research indicates that offspring born to smoking parents face compounded reproductive health challenges [12]. While animal studies are useful, especially from a mechanistic and ethical perspective (as human studies tend to be retrospective or cohort in nature), it is a common challenge to draw definitive conclusions and direct comparisons to humans. Variability in experimental protocols, including differences in dosage, duration, and timing of exposure, further complicates the interpretation and clinical relevance of results.

This systematic review provides the first known comprehensive analysis of the studies reporting the effects of parental smoking on offspring reproductive health. With a focus on maternal and paternal influences, their combined impact, and dose-response relationships, it assesses the reliability of animal models, explores mechanisms, such as genetic and epigenetic damage, and identifies critical exposure thresholds.

2. Materials and Methods

2.1. Eligibility Criteria

This systematic review utilised comprehensive database searches, PRISMA-guided screening, and data extraction to ensure transparency and minimise bias in analysing eligible studies.

2.2. Search Strategy

Articles were sourced from three databases: PubMed, Web of Science, and Scopus. Each database was filtered to include only articles published in English and to exclude reviews. The key terms used were as follows: 1) smoking terms: “smoke,” “nicotine,” “tobacco, “cigarette, “e-cigarette, “JUUL. 2) time of exposure: “prenatal, “maternal, “during pregnancy, “perinatal, “lactation, “fetal exposure. 3) Effect on offspring: “offspring, “infant, “boy, “girl, “male, “female, “age groups, “son, “newborn, “in vitro, “children. 4) Reproductive health: “reproductive outcome, “reproductive hormone, “semen quality, “secondary sex, “reproductive parameters, “genital development, “testis development, “sperm count, “oogonia, “sexual behavior, “genital anogenital, “reproductive disorders, “long-term fertility, “ovarian reserve. See supplement Table 1 for detailed search terms.

The search was conducted on March 18th, 2025, yielding a total of 2,553 articles: PubMed (684), Web of Science (479), and Scopus (1,390). A total of 949 duplicates were then removed using EndNote software. The remaining titles and abstracts (1,604) were manually scanned for relevance to the effect of parental smoking on offspring’s reproductive outcomes. This scanning process was validated by an independent reviewer. The remaining articles then had their full texts screened and were evaluated for inclusion in the study using the inclusion/exclusion criteria outlined in Table 1. Thirty-one studies met these eligibility criteria and so were included in this systematic review. A PRISMA 2020 flow diagram detailing the process of this systematic review is shown in Figure 1.

Table 1. The inclusion and exclusion criteria used to determine eligibility.

Inclusion Criteria	Exclusion Criteria
Human and animal studies on parental smoking and fetal reproductive health	Human and animal studies on parental smoking and non-reproductive outcomes (e.g., weight, cognitive or sexual behaviour)

Animal studies with quantifiable tobacco exposure	Studies on predictors of smoking, IVF outcomes cephalisation
Sex-specific effects in offspring	Non-research papers, protocols, letters, reviews or comments
Combined maternal and paternal smoking effects	
Peer-reviewed papers with measurable reproductive outcomes (e.g., hormones)	

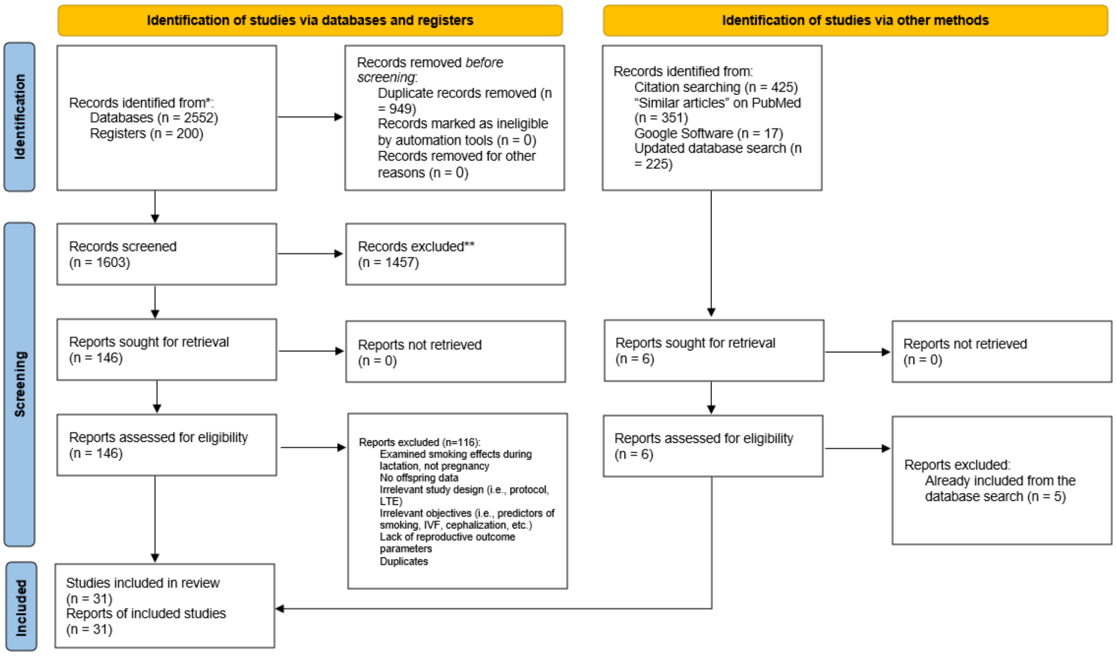

Figure 1. Prisma Flow diagram showing the detailed process of screening and study inclusion.

2.3. Data Extraction

Data extraction was conducted using a structured Excel spreadsheet. The data were exported into pre-defined tabular formats and categorised based on research characteristics, sources of smoking exposure, and outcomes. Coded data included the year of publication, study type, country of origin, number of participants, and detailed information on smoking exposure, such as the source (paternal, maternal, or both), material type, and dosage. Additional variables included study quality factors, reproductive function indicators (e.g., hormone levels, fertility indices, organ development), and offspring sex (male and/or female). The extracted reproductive endpoints encompassed hormonal assessments, semen quality, and other measures of human reproductive fitness. This structured rating system enabled a consistent comparison of study findings and their applicability. By consolidating the data, this approach facilitated the identification of common patterns and research gaps related to parental smoking and its impact on offspring reproductive health.

2.4. Quality Assessment

A customised scoring system was employed to evaluate the robustness of studies based on 16 parameters, such as sample size, intervention clarity, and outcome measurement (Table 2). Four aspects of the publications were assessed, namely the model system used, the sample quality (including sample size and controls), the methodology of the study, and the outcomes measured. The overall score was calculated by dividing the sum of the given scores by the total number of highest possible score.

Table 2. Scoring system to assess the robustness of included papers.

Category	Reasoning for Score
Model If multiple models are used combined score is given.	Human (n/2) Animal (n/1) Unclear (0)
Sample quality If multiple components are stated a combined score is given	Unknown (0) Defined Controls (n/1) Sample Size (n/2); where sex and participant number (n/1) and sample size is justified and/or dropout data from sample is mentioned (n/1) Representative sample (n/3); whether study reflects the characteristics of the larger population. Study type (n/1) (i.e: randomised control), demographics of participants (age, gender and ethnicity) (n/1), paper specifies who was included/excluded and why (n/1) **In animals: information on strain and age (n/1), housing and ethical approval (n/1) randomization and blinding (n/1)*
Methodological quality	Unknown (0) Smoking Material in humans (n/1)* **In animals' type of administration and material (n/1)* Source of Smoking: Maternal (n/1), Paternal (n/1), Both (n/2) Unknown (0) **In animals -> indirect exposure-passive smoking* Smoking Dose (n/1) Hormone assessment (n/1)
Measured outcomes If multiple components are stated a combined score is given	Semen Parameters (WHO parameters: semen volume, count, motility and morphology) (n/1) Any other measurements (oogonia, somatic cell, testis size, Angiogenetal distance, time at puberty, age of menarche) (n/1) >than three reproductive fitness measures (n/3)

3. Results

Thirty-one articles were included in the final analysis of the systematic review based on their inclusion criteria. Most of these studies examined the impact of maternal smoking (19 studies), followed by paternal smoking (5 studies), dual-parental smoking (3 studies). Moreover, environmental tobacco smoke or other indirect exposures (referred to as passive source) were also the topic of interest in 4 studies. These articles comprised human observational studies, animal experiments, and a few studies involving both humans and animals.

3.1. Impact of Maternal Cigarette Smoke Exposure on Offspring Reproductive Health

There were 19 studies examining the effect of maternal smoking on offspring reproductive health (Table 3), with several studies highlighting an association between smoking while pregnant and adverse effects on the reproductive health of offspring. Numerous studies identified low sperm concentration and motility and alteration in the levels of testosterone. For instance, Ramlau-Hansen et al. (2007) and Ravnborg et al. (2011) observed that male babies born to smoking mothers had poor sperm quality and precocious puberty [13,14]. The baseline characteristics of included studies focusing on maternal smoking impact on offspring are summarized in Table 3.

Maternal smoking was mainly associated with adverse reproductive outcomes in male offspring. Testis size, a critical indicator of reproductive capacity, was consistently reduced in male offspring of smokers. For instance, Jensen, 2004 observed that the mean testis volume in the smoking group was 19.1 mL (SD: 4.4), compared to 21.3 mL (SD: 5.0) in the non-smoking group [15]. This difference was statistically significant ($p < 0.01$), reinforcing the link between prenatal exposure and

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impaired testicular development. Similarly, semen volume was slightly reduced in the smoking group, with a mean of 3.0 mL (SD: 1.5) compared to 3.1 mL (SD: 1.5) in the non-smoking group, suggesting early developmental insults to reproductive structures. Sperm quality metrics, including testis volume at birth, concentration and motility, were also negatively impacted by maternal smoking. Whether mothers smoked only during pregnancy or continued smoking after birth is not explicitly stated in studies. Ramlau-Hansen, 2007, examined maternal smoking of more than 19 cigarettes per day, resulting in a mean sperm concentration of 2.6 million/mL (SD: 1.7), significantly lower than the 3.3 million/mL (SD: 2.5) observed in the non-smoking cohort [13]. Total sperm count followed a similar trend, with smoking groups reporting counts as low as 69 million compared to 98 million in non-smoking groups. This substantial reduction revealed the dose-dependent nature of the impact of smoking on spermatogenesis.

Maternal smoking also significantly influenced hormonal profiles in male offspring, with testosterone and estradiol levels showing notable deviations [16]. Ramlau-Hansen (2008) reported lower free testosterone levels in male offspring exposed to maternal smoking, with a mean of 16.4 nmol/L (95% CI: 13.3–19.4) compared to 16.7 nmol/L (95% CI: 14.1–20.3) in non-smoking groups [17]. Estradiol levels were similarly affected, with smoking groups exhibiting reduced concentrations (mean: 25.2 pg/mL, SD: 19.9) compared to nonsmokers (mean: 27.2 pg/mL, SD: 21.8). Elevated sex hormone-binding globulin (SHBG) levels in smoking-exposed offspring suggest disruptions in androgen bioavailability and hormonal balance, with SHBG levels significantly higher in smokers (mean: 9.2 nmol/L, SD: 5.5) versus nonsmoker (mean: 6.6 nmol/L, SD: 4.0).

Studies on female offspring revealed notable effects on pubertal timing and hormonal development. Zhang, 2015 reported delayed menarche in daughters of smokers, with a mean age of 13.02 years (95% CI: 12.66–13.39) compared to 13.17 years (95% CI: 12.77–13.58) in nonsmokers [18]. In animal study by Erdem Guzel, 2020 maternal tobacco smoke advanced the onset of puberty in the female offspring. [19] Brix, 2019 found significant reductions in Tanner breast and pubic hair staging times, with breast stage 4 occurring approximately 2.8 months earlier in smoking-exposed daughters compared to non-exposed peers ($p < 0.001$) [20]. These findings revealed the sex-specific nature of smoking's impact, with maternal smoking disproportionately affecting male reproductive metrics and paternal smoking influencing female hormonal profiles.

Anogenital distance (AGD) was another key metric affected by maternal smoking. Fowler, 2011 reported shorter AGD measurements in male fetuses exposed to maternal smoking (mean: 17.6 mm, SD: 2.5) compared to non-smoking groups (mean: 13.9 mm, SD: 2.3) [21]. In contrast, female offspring exhibited longer AGD in smoking groups, as reported by Kızılay, 2021 (mean: 14 mm, SD: 2.5) compared to nonsmoker (mean: 13.1 mm, SD: 2.2) [22]. In the cohort study by Cirillo, 2011, maternal smoking during pregnancy was associated with a higher risk of cryptorchidism (aHR = 1.18, 95% CI: 1.12, 1.24) in male offspring [23]. These findings indicate that maternal smoking exposure disrupts sexually dimorphic development, with implications for reproductive health and disease risk.

Dose-response analyses highlighted the proportional relationship between cigarette consumption and reproductive outcomes. Higher maternal smoking doses (>19 cigarettes/day) consistently resulted in more significant reductions in sperm concentration, testis size, and hormonal levels compared to lighter smoking (<10 cigarettes/day). For example, Ramlau-Hansen, 2007 reported that heavy maternal smoking reduced total sperm count by 30–40% compared to nonsmokers [13].

Table 3. A descriptive summary of included studies focusing on the impact of maternal smoking of offspring.

First author and year (citation number)	Study Design	Model	Method	Sample Size	Smoking Material	Source of Smoking	Smoking Dose	Offspring Sex
Adamcová, 2017 [16]	Case-control study	Human	Changes in production of steroid hormones in pregnant smokers	88 healthy women (17 active smokers and 71 non-smokers)	Cigarette	Maternal	6-25 day	Both (Male & Female
Brix, 2019 [20]	Population-based study	Human	15,819 children (7,696 male offspring and 8,123 daughters) who were part of the Puberty Cohort, a sub cohort of the Danish National Birth Cohort	15,819 children participated in the study	Cigarette tobacco	Maternal during pregnancy	nonsmoker, light-smoker (1–10 daily cigarettes), heavy-smoker (>10 daily cigarettes)	Both (Male & Female)
Brix, 2019 [24]	Population-based study	Human	42,849 of 56,641 eligible boys and girls from the Danish National Birth Cohort born between 2000 and 2003	42,849 children after exclusions	Cigarette tobacco	Maternal smoking during the first trimester of pregnancy	nonsmoker, stopped smoking, 1-9 cigarettes /day, 10-14 cigarettes/day, 15+ cigarettes/day	Both (Male & Female)
Cirillo, 2011 [23]	Retrospective cohort	Human	Girls aged 6–11 years from the Third National Health and Nutrition Examination Survey (NHANES III).	705 girls with complete LH hormone measurements; of these, 689 had complete inhibin B analysis.	Cigarette	Maternal during pregnancy	Mean (SD) = 15.5 (9.7)	Male
Erdem Guzel, 2020 [19]	Experimental study	Rats	Female rat offspring	28 Sprague-Dawley female rats	Tobacco	Maternal	20g of tobacco per/day	Female
Fowler, 2009 [25]	Observational study	Human	In total, 46 fetuses were used to determine circulating hormones and cotinine levels from cardiac blood	46 mothers and fetuses.	Tobacco	Maternal during pregnancy	Mean (SD) = 12 (1). 12/day = heavy smoking	Male
Fowler, 2011 [21]	Retrospective cohort	Human	83 electively terminated, normally progressing, second-trimester fetuses (11 to 20 weeks' gestation)	83 fetuses	Cigarette tobacco	Maternal during pregnancy	Unknown	Male
Gollenberg, 2015 [26]	Retrospective study	Human	Girls aged 6–11 years from the Third National Health and Nutrition Examination Survey (NHANES III).	705 female offspring (girls 6-11 years)	Cigarette smoke	Maternal during pregnancy and current environmental tobacco smoke (ETS) exposure	Unknown	Female
Gordon, 2022 [27]	Prospective cohort	Human	>18 years old with a singleton pregnancy with female fetus	64 female infants	Self-reported smoking	Maternal	Active smoker (>=1/2 pack/day)	Female
Hærvig, 2022 [28]	Retrospective study	Human	Pregnant women	984 male offspring	Cigarette smoke	Maternal	Light (=< 10 cigarettes/day); Heavy smokers (>10 cigarettes/day)	Male

Jensen, 2004 [15]	Follow-up study	Human	Young men from general populations undergoing military examination	889 (Denmark), 221 (Norway), 313 (Finland), 157 (Lithuania), 190 (Estonia)	Tobacco	Maternal, during foetal life	Light smoking (1-9 cigarettes/day); Medium smoking (10-19 cigarettes/day); Heavy smoking (>=20 cigarettes/day)	Male
Kızılay, 2020 [22]	Prospective case-control study	Human	120 infants (56 female and 64 male) from mothers who smoked during pregnancy and a control group of 120 infants (56 female, 64 male) whose mothers had no active or passive smoke exposure	240 infants evaluated, 120 in the study group (56 female and 64 male), and 120 in the control group (56 female, 64 male) included in the study after exclusions	Cigarette tobacco	Maternal during pregnancy	Unknown	Both (Male & Female)
Lindbo, 2022 [29]	Register-based, sibling-matched cohort	Human	823,670 live-born, singleton boys born in Denmark between January 1st, 1991, and December 31st, 2016	823,670 singleton boys	Cigarette tobacco	Maternal during pregnancy	(=<5, 6-10, 11-20, and >=21 cigarettes/day)	Male
Lutterodt, 2009 [30]	Prospective study	Human	First-trimester women >18 years of age	28 Fetuses	Cigarette smoke		1-5, 6-10, 11-15 16-20 cigarettes/day	Both (Male & Female)
Mamsen, 2010 [31]	Prospective study	Human	First-trimester women >18 years of age	24 Fetuses (embryonic testes)	Cigarette smoke		Ranging from 1 to 25	Both (Male & Female)
Ramlau-Hansen, 2007 [13]	Follow-up study	Human	male offspring of Mothers in the Healthy Habits for Two cohort	347 men	Tobacco		Unknown	Male
Ramlau-Hansen, 2008 [17]	Population-based follow-up study	Human	male offspring of mothers in 'Healthy Habits for Two' cohort	347 men	Tobacco		Light smoking (1-9 cigarettes/day); Medium smoking (10-19 cigarettes/day); Heavy smoking (>=20 cigarettes/day)	Male
Ravnborg, 2011 [14]	Semen-quality study	Human	4862 Danish men from the Copenhagen area	3486 men	Tobacco		Light smoking (1-10 cigarettes/day); Heavy smoking (>10 cigarettes/day)	Male
Zhang, 2015 [18]	Retrospective study	Human	751 female students aged 8 to 20 years from a suburban district in Shanghai	751 girls included for data analysis after exclusions	Tobacco smoke		Unknown	Female

In summary, of the 19 studies examining maternal smoking, 14 studies examined the effect of maternal smoking in male offspring, and this was linked to adverse outcomes such as reduced sperm quality, disrupted gonadal development, hormonal imbalances and higher risk f cryptorchidism in the male offspring [13–17,29,32]. Female offspring were studied less, with only 5 studies, showing disrupted ovarian reserve and hormonal regulation [18,27]. Active maternal smoking during pregnancy was associated with lower testosterone levels, reduced anogenital distance (AGD), and delayed pubertal development in male offspring [21,25,32]. Environmental tobacco smoke (ETS) was also linked to hormonal disruptions in both sexes [22,26]. Hormonal changes included alterations in testosterone and estradiol levels. Fowler, 2009 and Fowler, 2011, demonstrated that maternal smoking during pregnancy reduced testosterone levels in male fetuses, impacting anogenital distance (AGD) and pubertal onset [22,25]. Gordon, 2022, observed increased maternal testosterone levels associated with active smoking, suggesting potential androgenic effects [27]. In contrast, Cirillo, 2011 observed no effect on male offspring semen quality associated with maternal smoking [23]. Studies on female offspring, including Zhang, 2015 and Gordon, 2022, linked maternal smoking to delayed pubertal onset and reduced ovarian reserve [18,27]. In animal study by Erdem Guzel, 2020 found that maternal tobacco smoke advanced onset of puberty in female offspring, an increase of addition apoptotic cell markers in the rat ovary [19]. The variability in findings was compounded by inconsistent definitions and classifications of smoking exposure. While most studies outlined specific smoking dose ranges, five studies lacked precise categorisation, obscuring dose-response relationships.

A customized scoring system was then employed to evaluate the robustness of studies based on 16 parameters, such as sample size, intervention clarity, and outcome measurement. Of the 19 studies examining the effect of maternal smoking on offspring health, scores were relatively high, ranging from 0.438 to 0.75 (Table 4). Human studies consistently scored higher, with Ravnborg 2011 achieving a score of 0.750 due to its large sample size, detailed exposure classifications, and comprehensive reproductive outcomes [14]. Fowler, 2009 and Hærvig, 2022 scored 0.688, reflecting their strengths in longitudinal design and standardized methodologies (Table 4) [25,28].

doi:10.20944/preprints202507.0028.v1

Table 4. A summary of the sample and methodological quality of each maternal smoking study included in this systematic review. The overall score was calculated by dividing the sum of the given scores by the total number of highest possible scores.

First author and Year (Citation number)	Sample Quality		Methodological quality					Measured Outcomes (>two reproductive measured outcome n/3)			Overall quality Score
	Sample Size (n/2)	**Defined controls (n/1)**	**Hormonal (n/1)**	**Semen Parameters (n/1)**	**Morphological assessment of oocytes or any other measurements (n/1)**	**Representative sample (n/3)**	**Model (n/2)**	**Smoking Material (n/1)**	**Source of Smoking (n/1)**	**Smoking Dose (n/1)**	
Adamcová (2017) [16]	Unclear, 919 cases (1)	Yes (1)	Yes (1)		-	Unknown (0)	Human (2)	Cigarette (1)	Paternal smoking before conception (1)	Mean (SD) = 17.14 (7.95). (1)	0.5
Brix (2019) [24]	Unclear, 42849 children (1)	Yes (1)	-	-	Yes (1) pubic hair and genital stage	13 years in boys and 11 years in girls (2)	Human (2)	Cigarette tobacco (1)	Maternal smoking during pregnancy (1)	Unknown (0)	0.563
Cirillo (2011) [23]	Unclear, 705 girls (1)	Yes (1)	-	Yes (1)	-	Age 6-11 years (2)	Human (2)	Cigarette (1)	Maternal smoking during pregnancy (1)	Mean (SD) = 15.5 (9.7). (1)	0.625
Erdem Guzel (2020) [19]	Unclear, 28 rats (1)	Yes (1)	Yes (1)		-	Unknown (0)	Rats (1)	Unknown (0)	Unknown (0)	Unknown (0)	0.25
Fowler (2009) [25]	Unclear, 347 men (1)	Yes (1)	Yes (1)	-	Yes (1)	Age: 18-21 years (2)	Human (2)	Tobacco (1)	Maternal during pregnancy (1)	Mean (SD) = 12 (1). (1)	0.688
Fowler (2011) [21]	Unclear, 83 fetuses (1)	Yes (1)	-	-	Yes (1) testis size and AGD	Unknown (0)	Human (2)	Cigarette tobacco (1)	Maternal during pregnancy (1)	Unknown (0)	0.44
Gollenberg (2015) [26]	Unclear, 705 girls (1)	Yes (1)	Yes (1)		-	Age range 6-11 years (2)	Human (2)	Cigarette (1)	Maternal smoking during pregnancy and current environmental tobacco smoke (ETS) exposure. (1)	Unknown (0)	0.563
Gordon (2022) [27]	Unclear, 62 singleton female (1)	Yes (1)	-	-	Yes (1)	Unknown (0)	Human (2)	Self-reported smoking (1)	Maternal (1)	Active smoker (>=1/2 pack/day). (1)	0.5
Hærvig (2022) [32]	Unclear, 984 sons (1)	Yes (1)	Yes (1)	Yes (1)	-	Age at clinical visit 19.3 (5.3) years (2)	Human (2)	Cigarette smoke (1)	Maternal (1)	Light (=< 10 cigarettes/day); Heavy smokers (>10 cigarettes/day). (1)	0.688
Jensen (2004) [15]	Unclear, 1770 (1)	Yes (1)	-	Yes (1)	Testis Volume (1)	Men aged 16-27 years (2)	Human (2)	Tobacco (1)	Maternal, during fetal life (1)	Light smoking (1-9 cigarettes/ day); Medium smoking (10-19	0.688

										cigarettes/day); Heavy smoking (>=20 cigarettes /day). (1)	
Kızılay (2021) [22]	Unclear, 240 infants (1)	Yes (1)	-	-	Yes (1)	Unknown (0)	Human (2)	Cigarette tobacco (1)	Maternal during pregnancy (1)	Unknown (0)	0.437
Lindbo (2022) [29]	Unclear, 823,670 singleton (1)	Yes (1)	-		Yes (1)	Boys diagnosed with cryptorchidism or hypospadias (2)	Human (2)	Cigarette tobacco (1)	Maternal smoking during pregnancy (1)	(=<5, 6-10, 11-20, and >=21 cigarettes/day). (1)	0.563
Lutterodt (2009) [30]	Unclear, 28 fetuses (1)	Yes (1)	-	-	Yes (1)	38-64 days of age (2)	Human (2)	Cigarette smoke (1)	Maternal (1)	1-5, 6-10, 11-15, and >16 cigarettes/day. (1)	0.625
Mamsen (2010) [31]	Unclear, 24 fetuses (1)	Yes (1)	-	-	Yes (1)	37-68 days of age (2)	Human (2)	Cigarette smoke (1)	Maternal (1)	Ranging from 1 to 25. (1)	0.625
Ramlau-Hansen (2007) [13]	Unclear, 347 men (1)	Yes (1)	-	Yes (1)	Testis Volume (1)	Age: 18-21, Gender: Male, (2)	Human (2)	Tobacco (1)	Maternal (1)	Unknown (0)	0.625
Ramlau-Hansen (2008) [17]	Unclear, 347 men (1)	Yes (1)	Yes (1)	-		Age: 18-21 years, Gender: Male (2)	Human (2)	Tobacco (1)	Maternal (1)	Light smoking (1-9 cigarettes/ day); Medium smoking (10-19 cigarettes/day); Heavy smoking (>=20 cigarettes /day). (1)	0.625
Ravnborg (2011) [14]	Unclear, 3486 men (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1) Cryptorchidism and testis size	Men aged 19.4 years (mean/median) (2)	Human (2)	Tobacco (1)	Maternal, in utero exposure (1)	Light smoking (1-10 cigarettes /day); Heavy smoking (>10 cigarettes /day). (1)	0.75
Zhang (2015) [18]	Unclear, 751 girls (1)	Yes (1)	-	-	Yes (1) menarche age	Unknown (0)	Human (2)	Tobacco smoke (1)	Maternal passive smoking during pregnancy (1)	Unknown (0)	0.438

3.2. Impact of Paternal Cigarette Smoke Exposure on Offspring Reproductive Health

Five studies investigated paternal smoking on reproductive health and revealed effects on offspring health comparable to those observed with maternal smoking. Table 5 summarizes the baseline characteristics of these studies assessing the impact of paternal smoking on offspring.

The primary mechanisms through which paternal smoking affects offspring appear to be genetic and epigenetic, particularly through alterations occurring during spermatogenesis. Multiple studies [33–36,38] have found that paternal smoking is associated with reduced sperm quality, shortened reproductive lifespan and altered testosterone levels Specifically, Haervig, 2023 reported that male offspring of pre-conceptional smokers had lower semen quality [34]. For example, the percentage of progressive spermatozoa was slightly lower in the smoking group (63%, SD: 29) compared to non-smoking groups (64%, SD: 30). More notably, total sperm count showed a substantial difference, with smokers' offspring having a mean count of 130 million (SD: 111) versus 230 million (SD: 225) in non-smokers. Hormonal indicators also reveal detrimental effects. Inhibin B, a marker of spermatogenic activity, was also lower among sons of smokers (mean: 191 pg/mL, SD: 88) versus non-smokers (mean: 204 pg/mL, SD: 98). While individual studies have shown negative impacts, an updated and republished metanalysis of 867 young adult men found no overall association between paternal preconception smoking and semen parameters or testicular size [35]. In females, data from Fukuda (2011) suggest that smoking reduces the reproductive lifespan by leading to earlier menopause ($P = .059$) [37].

In summary, of the 5 studies examining paternal smoking, only one study examined the effect of paternal smoking in female offspring, and four of the studies examined male offspring, with effects appearing to be genetic, epigenetic and hormone related.

As above, a customized scoring system was employed to evaluate the robustness of studies based on 16 parameters, such as sample size and intervention clarity (Table 6). Again, human studies consistently scored higher, with Fukuda, 2011 achieving a score of 0.5363 due to its large sample size, detailed exposure classifications, and comprehensive reproductive outcomes [34,35,38] scored 0.438, reflecting their strengths in longitudinal design and standardized methodologies (Table 6). Most of studies focusing on parental smoking had mid-level overall quality score, ranging from 0.438 to 0.563.

doi:10.20944/preprints202507.0028.v1

Table 5. Baseline characteristics of studies examining the impact of paternal smoking on offspring.

First author and year (citation number)	Investigation Period	Study Design	Model	Method	Sample Size	Smoking Material	Smoking Dose	Source of Smoking	Offspring Sex
Fukuda, 2011 [37]	June 2007 to December 2009	Observational study	Human	1,093 postmenopausal women attending clinics for gynecological assessment	1,093 daughters out of 1,164 approached	Cigarette tobacco	Unknown	Paternal smoking around the time of conception	Female
Haervig, 2020 [38]	1996-2003	Population-based follow-up study within the Danish National Birth Cohort	Human	Adult male offspring born to mothers included in the DNBC	772 participated, 751 included for analysis after exclusions	Cigarette tobacco	Unknown	Paternal during and potentially before pregnancy	Male
Haervig, 2023 (originally published) [34]	2017–2019	Retrospective study	Human	867 young adult men from the Danish National Birth Cohort	867 male offspring after exclusions	Self-reported smoking	Unknown	Paternal pre-conceptional smoking reported by pregnant women	Male
Hærvig, 2025 (republished, re-run analysis) [35]	2017–2019	Retrospective cohort (reran analysis from 2023)	Human	867 young adult men from the Danish National Birth Cohort	867 male offspring after exclusions	Self-reported smoking	Unknown	Paternal during gestational week 16	Male
Pabarja, 2021 [36]	Unknown	Observational study	Mice	25 adult NMRI mice (19 females and 6 male) aged 8–10 weeks		Injection	Control—saline solution	Paternal during and potentially before pregnancy	Male

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Table 6. A summary of the sample and methodological quality of each paternal smoking study included in this systematic review. The overall score was calculated by dividing the sum of the given scores by the total number of highest possible scores.

	Sample Quality					Methodological quality		Measured Outcomes (>two reproductive measured outcome n/3)			
First author (Year) Citation number	**Sample Size (n/2)**	**Defined controls (n/1)**	**Hormonal (n/1)**	**Semen Parameters (n/1)**	**Morphological assessment of oocytes or any other measurements (n/1)**	**Representative sample (n/3)**	**Model (n/2)**	**Smoking Material (n/1)**	**Source of Smoking (n/1)**	**Smoking Dose (n/1)**	**Overall quality Score**
Fukuda (2011) **[37]**	Unclear, 1,093 daughters (1)	Yes (1)	-	-	Yes (1)	Daughters' ages at menarche (13.8 years) (2)	Human (2)	Cigarette tobacco (1)	Paternal smoking around the time of conception (1)	Unknown (0)	0.563
Haervig (2020) **[38]**	Unclear, 772 participants (1)	Yes (1)		Yes (1)	-	Unknown (0)	Human (2)	Tobacco (1)	Paternal during and potentially before pregnancy (1)	Unknown (0)	0.438
Haervig (2023) **[34]**	Unclear, 867 sons (1)	Yes (1)	-	Yes (1)	-	Unknown (0)	Human (2)	Tobacco (1)	Paternal pre-conceptional smoking reported by pregnant women around gestational week 16. (1)	Unknown (0)	0.438
Haervig (2025) **[35]**	Unclear, 867 sons (1)	Yes (1)	Yes (1)	Yes (1)	-	Unknown (0)	Human (2)	Tobacco (1)	Paternal pre-conceptional smoking reported by pregnant women around gestational week 16. (1)	Unknown (0)	0.438
Pabarja (2021) **[36]**	Unclear, 772 participants (1)	Yes (1)	-	Yes (1)	-	Unknown (0)	Human (2)	Tobacco (1)	Paternal during and potentially before pregnancy (1)	Unknown (0)	0.438

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3.3. Impact of Dual Parental Smoking on Offspring

Three studies examined dual-parental smoking, together suggesting an additive or even synergistic effect on offspring outcomes. The baseline characteristics of these studies are summarised in Table 7.

Ernst, 2012 and Axelsson, 2013 reported compounded reductions in sperm quality, heightened hormonal disruptions, and increased developmental abnormalities in offspring when both parents smoked [39,40]. These findings underscore the distinct and severe impact of dual-parental smoking, emphasising the need for targeted public health interventions. The combined genetic, epigenetic, and environmental exposures from both parents further amplify these risks. Axelsson 2013 and Axelsson, 2018 linked dual-parental smoking to disrupted reproductive hormone levels and altered gonadal morphology [33,40]. Addressing dual-parental smoking is crucial for mitigating cumulative reproductive health risks and improving offspring outcomes.

Axelsson, 2013 also observed reductions in semen quality, with total sperm count significantly lower in dual-smoking households (mean: 85 million, SD: 27) compared to households where neither parent smoked (111 million, SD: 40) [40]. Sperm motility was also impaired, with motile sperm percentages averaging 50% (SD: 17) in dual-smoking households versus 54% (SD: 19) in non-smoking households. Hormonal disruptions were more significant in offspring exposed to dual-parental smoking. Elevated SHBG levels and altered free testosterone-to-estradiol ratios suggest compounded effects on androgen and estrogen balance. For instance, SHBG levels were significantly higher in dual-smoking groups (mean: 10.1 nmol/L, SD: 5.7) compared to single-parent smoking households (mean: 7.6 nmol/L, SD: 4.9), the sex was not specified.

Table 7. A descriptive summary of included studies focusing on the impact of dual-parental smoking on offspring.

First author [Ref]	Investigation Period	Study Design	Model	Method	Sample Size	Source of Smoking	Smoking Material	Smoking Dose	Offspring Sex
Axelsson, 2013 [40]	2008–2010	Retrospective cohort	Human	295 adolescents from the general population near Malmö, Sweden, recruited for the study	295 men included after exclusions	Maternal and paternal	Cigarette smoke	1-9 or >=10 cigarettes/day	Male
Axelsson, 2018 [33]	2008 to 2010	Population-based study	Human	Men aged 17–20 years from the general Swedish population	104 men	Maternal and paternal (during pregnancy and current own smoking)	Cigarette smoke	Average of 6.6 cigarettes/day	Male
Ernst, 2012 [39]	2008-2009	Follow-up study	Human	Danish pregnancy cohort Non-exposed = 226, Low- exposed= 67, High exposed+69	362 daughters and mothers	Maternal and paternal (during pregnancy and current own s	Cigarette smoke	Low-exposed (0-9 cigarettes/ day); High-exposed (>=10 cigarettes/ day)	Female

In summary, Ernst et al. 2012, Axelsson et al. 2013 and Axelsson et al. 2018 highlighted that the combined smoking of both parents intensified cuts in sperm quality and hormonal imbalance [33,39,40]. Comparison across studies was again confounded due to the variability of smoking doses for each study.

Again, a customised scoring system was employed to evaluate the robustness of studies based on 16 parameters. Axelsson 2018 achieved lowest score (0.5), Ernst, 2012 and Axelsson, 2013, achieved moderate scores (0.625) due to their use of representative samples (Table 8) [33,39,40].

Table 8. A summary of the sample and methodological quality, and measured outcomes, of each dual paternal smoking study included in this systematic review. The overall score was calculated by dividing the sum of the given scores by the total number of highest possible scores.

First author (Year)	Sample Quality			Methodological quality				Measured Outcomes (>two reproductive measured outcome n/3)			
	Sample Size (n/2)	Defined controls (n/1)	Representative sample (n/3)	Model (n/2)	Smoking Material (n/1)	Source of Smoking (n/1)	Smoking Dose (n/1)	Hormonal (n/1)	Semen Parameters (n/1)	Morphological assessment of oocytes or any other measurements (n/1)	Overall quality Score
Axelsson (2013) **[40]**	Unclear, 295 men (1)	Yes (1)	Mean age of 18 years, BMI of 23 kg/m2 (2)	Human (2)	Cigarette smoke (1)	Maternal and paternal during pregnancy, and current own smoking (1)	1-9 or >=10 cigarettes/day. (1)	—	Yes (1)	-	**0.625**
Axelsson (2018) **[33]**	Unclear, 104 men (1)	Yes (1)	Unknown (0)	Human (2)	Cigarette smoke (1)	Parental (maternal and paternal) smoking at the time of pregnancy (1)	Average of 6.6 cigarettes/day. (1)	—	Yes (1)	-	**0.5**
Ernst (2012) **[39]**	Unclear, 295 adolescents (1)	Yes (1)	Mean/median age: 19.4/19.0 years (2)	Human (2)	Cigarette smoke (1)	Maternal and paternal during pregnancy, and current own smoking (1)	Low-exposed (0-9 cigarettes /day); High-exposed (>=10 cigarettes/day). (1)	Yes (1)	-	-	**0.625**

3.4. Impact of Passive Smoke Exposure on Offspring Reproductive Health

The final section of this systematic review focuses on passive smoking, where only animal models were used. Table 9 summarises the baseline characteristics of these studies, along with the types of offspring affected [41–44]. Al-Sawalha, 2021 found elevated oxidative stress markers and reduced testosterone levels in rats exposed to waterpipe tobacco smoke, underscoring the generalizability of smoking's reproductive effects across species [44]. Another animal study found that nicotine exposure reduced AGD at birth of both male and female offspring; however, by 34 days of age, this change was no longer apparent [42]. Camlin, 2016 examined only female offspring and observed a reduced oocyte quality, abnormal levels of cellular proliferation and decreased interaction with wild-type sperm [41].

Lastly, Oyeyipo, 2018 demonstrated that male rat offspring exposed to maternal nicotine exhibited significantly reduced foetal testis weight (mean: 21 mg, SD: 1) compared to controls (mean: 26 mg, SD: 4) [43].

Table 9. Baseline summary of studies examining the impact of passive smoking (animal models) on offspring.

First author, year Citation	Investigation Period	Study Design	Model	Method	Sample Size	Source of Smoking	Smoking Material	Smoking Dose	Offspring Sex
Al-Sawalha, 2021 [44]	Unknown	Experimental study	Wistar rats	Male progeny of lactating rats exposed to waterpipe tobacco smoke (WTS) or fresh air	Not explicitly mentioned; derived from 22 lactating dams divided into two groups	Passive	Waterpipe tobacco smoke	1 hour twice/day	Male
Camlin, 2016 [41]	Unknown	Retrospective cohort	Mice	Six-week-old female mice	4 mice	Passive	Exposure to mainstream cigarette smoking	12 cigarettes /day	Female
Gyekis, 2010 [42]	2010	Experimental study	Mice	Pregnant C57B/6J mouse dams	291 mice (141 females, 150 males) were measured at birth for anogenital	Passive	Nicotine administered in drinking water at a	Unknown	Both (male & female)

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				and their pups	distance and body weight. 198 were measured at weaning, and 40 mice were included in the analysis at 34 days of age		concentration of 50 μg/ml		
Oyeyipo, 2018 **[43]**	Unknown	Experimental study	Wistar rats	F1 generation offspring of Wistar rats	Groups with 6 rats each for various treatment phases	Passive	Nicotine administered orally	Unknown	Male

Animal studies generally scored lower due to smaller sample sizes and inconsistent exposure definitions. In fact, in four studies, the methods were either not clearly described or involved the use of alternative to cigarette smoke (waterpipe tobacco). Camlin, 2016 and Oyeyipo, 2018 scored 0.563 and 0.438, respectively, indicating limitations in replicability and statistical power (Table 10) [41,43]. In studies reporting passive smoking in animal models, scores were relatively high, ranging from 0.375 to 0.563.

Table 10. The overall score was calculated by dividing the sum of the given scores by the total number of highest possible scores. The overall score was calculated by dividing the sum of the given scores by the total number of highest possible scores.

	Sample Quality			**Methodological quality**					**Measured Outcomes (>two reproductive measured outcome n/3)**		
First author (Year)	**Sample Size (n/2)**	**Defined controls (n/1)**	**Representative sample (n/3)**	**Model (n/2)**	**Smoking Material (n/1)**	**Source of Smoking (n/1)**	**Smoking Dose (n/1)**	**Hormonal (n/1)**	**Semen Parameters (n/1)**	**Morphological assessment of oocyte any other measurements (n/1)**	**Overall Score**
Al-Sawalha (2021) **[44]**	Unclear, 22 rats (1)	Yes (1)	Adult male progeny rats (2)	Wistar rats (1)	Waterpipe tobacco smoke (1)	Passive (1)	1 hour twice/day. (1)	Yes (1)	—	-	0.563
Camlin (2016) **[41]**	Unclear, 4 mice (1)	Yes (1)	6-week-old mice (2)	Mice (1)	Exposure to mainstream cigarette smoking (1)	Passive (1)	12 cigarettes/day. (1)	-	-	Yes (1)	0.563
Gyekis (2010) **[42]**	Unclear, 29 mice (1)	Yes (1)	Unknown (0)	Mice (1)	Nicotine administered in drinking water at a concentration of 50 μg/ml (1)	Passive (1)	Unknown (0)	—	-	Yes (1)	0.375
Oyeyipo (2018) **[43]**	Unclear, 6 rats (1)	Yes (1)	Unknown (0)	Wistar rats (1)	Nicotine administered orally (1)	Passive (1)	Unknown (0)	Yes (1)	Yes (1)	-	0.438

4. Discussion

The systematic review revealed the significant adverse effects of parental cigarette smoke exposure on offspring reproductive health, as evidenced by 31 studies. Maternal smoking was the most extensively studied, consistently linked to reduced sperm density, motility, hormonal imbalances, and impaired gonadal development in male offspring. Paternal smoking, though less frequently investigated, demonstrated similar negative effects mediated through sperm genetic and epigenetic pathways. Dual-parental smoking exhibited a compounded effect, amplifying reductions in sperm quality and endocrine disruptions in offspring. While animal models provided mechanistic insights, challenges such as dose standardisation and interspecies variability limited their translational relevance.

Overall, female offspring outcomes were underrepresented, leaving a critical void in understanding sex-specific reproductive risks. Future research should also prioritise standardising smoking dose definitions, conducting longitudinal studies with consistent exposure characterisation, and investigating both male and female offspring outcomes. Refinement of animal models with larger sample sizes and consistent dosing protocols is also essential to enhance translational relevance.

Emerging evidence in other areas points to a synergistic effect, where dual parental smoking leads to significantly higher risks to offspring health, such as increased risks of obesity and cardiovascular issues in adolescence and early adulthood [45]. Furthermore, there is an increasing likelihood that offspring will transition to daily smoking during adolescence and early adulthood when both parents smoke [46], suggesting a potential generational synergistic effect.

Similar to the effects of smoking, other environmental perturbations have also shown enhanced outcomes when both parents are equally exposed. Finger, 2015 reported that parental obesity negatively impacts pre-implantation mouse embryo development, including altered kinetics, morphology, and metabolism [47]. McPherson 2015, similarly emphasised that having two obese parents resulted in more detrimental impairments in embryo and fetal development when compared to either parent alone [48]. Ornellas, 2015 further demonstrated that diet-induced obesity in both parents contributes more to the programming of obesity and related comorbidities in the offspring than either parent individually [49]. Interestingly, studies have also shown how the effects of smoking can also persist across generations. A recent study by Watkins, 2022 demonstrated that grandmaternal smoking was associated with differential DNA methylation patterns in grandchildren, suggesting a long-term and potentially epigenetically-mediated intergenerational consequence [50]. Therefore, future research should focus on dual-parental influences, as they may have a greater impact on offspring reproductive and overall health across generations, as well as the underlying mechanisms involved.

A key strength of this review is its rigorous inclusion criteria, which ensured high-quality studies with clear exposure and outcome data. However, notable limitations include variability in smoking doses, reliance on self-reported data, and the exclusion of non-English studies and those published before 2000. These factors hindered the ability to perform robust meta-analyses and may have limited the breadth of findings. Additionally, small sample sizes and methodological inconsistencies in animal studies reduced their generalisability to human populations.

5. Conclusions

In conclusion, this systematic review shows the adverse effects of parental cigarette smoke exposure on offspring's reproductive health as influenced by sex and dose of exposure. Maternal smoking affects impaired semen quality, hormonal imbalance, and disruption of gonadal development in male offspring, and paternal smoking affects both male and female fertility, genetically and epigenetically. Second-hand smoke from both parents escalated these risks, showing an adverse interaction effect of parental smoking. From this perspective, it can be agreed that although the results of the given studies are conclusive, there was appreciable heterogeneity concerning study designs and smoking dose definitions, providing the basis for standardised research and specific, evidence-based public health initiatives. The following topics and issues that should be further examined include the use of new tobacco products (i.e., E-cigarettes), the methods of assessing exposure to tobacco products, and the effects of tobacco use on the multigenerational span.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org. Supplement Tables.

Author Contributions: LF: AW, VJ, AT and YA planned the systematic review design and reviewed the manuscript. YA undertook the systematic review, created the scoring system and wrote the manuscript.

Funding: This research was funded by The Ministry of Science and Education of Republic of Azerbaijan.

Data Availability Statement: The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author.

Acknowledgments: The University of Nottingham provided access to online libraries and services. We also wish to thank Dr Abdelaziz Abdelaal who validated the screening of publications. .

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

Abbreviation	Full Form
WHO	World Health Organization
PAHs	Polycyclic Aromatic Hydrocarbons
DOHaD	Developmental Origins of Health and Disease
AGD	Anogenital Distance
ETS	Environmental Tobacco Smoke
SHBG	Sex Hormone-Binding Globulin
SD	Standard Deviation

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