Pollutants and sperm quality: a systematic review and meta-analysis

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ABSTRACT

Male fertility and semen quality have declined over recent decades. Among other causes, exposure to environmental and occupational pollution has been linked to adverse reproductive outcomes, but effects on male semen quality are still uncertain. Therefore, the aim of the present study was to conduct a systematic review and meta-analysis to assess current evidence regarding the impact of exposure to tobacco smoke, environmental and occupational pollution on sperm quality in humans. In the meta-analysis, are included 22 studies showing that environmental and occupational pollutants may affect sperm count, volume, concentration, motility, vitality and sperm DNA and chromatin integrity. All included articles reported significant alterations in at least one of the outcomes studied in association with at least one of the pollutants studied. Considering that sperm quality can be considered a proxy for general health and that pollutants have a dramatic impact on climate change, it would be strongly recommended to better understand the role of pollutants on human, animal and planetary health.

Key words: Pollution, sperm quality, sperm parameters, male infertility

INTRODUCTION

Infertility is defined by the World Health Organization as the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse (WHO 2020). Although it is not possible to exactly estimate the global burden of infertility, a considerable number of people of reproductive age are infertile with a global estimated prevalence of 72.4 million (Boivin 2007). Male infertility is responsible, alone or in combination with female infertility, in approximately 50% of reported cases (Pizzol 2014). Several risk factors and causes might affect male fertility, including lifestyles, diabetes, obesity, hormonal diseases, testicular trauma, cryptorchidism, varicocele, genitourinary infections, ejaculatory disorders, chemo/radio or surgical therapies (Pizzol 2014). A decline in semen quality has been observed over recent decades; including a reduction in semen count, volume, motility, and morphology (Carlsen 1992). Consequently, WHO has lowered the accepted values for classic normal sperm parameters (Cooper 2010). Considering these remarkable changes over a relatively short period, it has been suggested that the decline in semen quality is most probably owing to environmental rather than genetic factors (Carlsen 1992). There is increasing concern about environmental factors associated with decreased sperm quality. Such factors may include exposure to tobacco smoke, polycyclic aromatic hydrocarbons (PAHs) or heavy metals, and air pollution (Harlev 2015; Deng 2016). The exposure to toxic pollutants which can be found in the environment, as well as occupational exposure to specific pollutants, due to job-related activities, have been demonstrated to negatively affect male fertility in humans (Kenz 2013; Jenardhanan 2016). Although a large body of evidence on the negative role of pollutants on sperm has been provided by in vitro studies, to date, little experimental clinical investigation has been performed in humans (Alamo 2019; Marchiani 2019). Moreover, to perform clinical studies on humans is challenging mainly due to the dosage and the length of exposure and the evaluation of other variables including drinking, overweight, obesity, social stress, and other diseases.

Given this background, the aim of this study was to conduct a systematic review and meta-analysis to assess current evidence regarding the impact of exposure to tobacco smoke, environmental and occupational pollution on sperm quality in humans.

METHODS

This systematic review adhered to the PRISMA (Liberati 2009) and MOOSE (Stroup 2000) statements and followed a structured protocol, available upon request to the corresponding author.

Data sources and literature search strategy

Two investigators (MT and DP) independently conducted a literature search using MEDLINE/PubMed, Scopus, CINAHL, Embase PsycINFO and Cochrane Library databases from inception until 31st of March 2020. Any inconsistencies were resolved by consensus with a third author (LS).

In PubMed, the following search strategy was used: “Pollution” OR “air pollution” OR “particulate matter” OR “diesel” OR “soot” OR “carbon” OR “black smoke” OR “dioxin” “smog” OR “traffic OR motor vehicles OR carbon dioxide/monoxide” OR “nitrogen dioxide/oxide” OR “ozone” OR “CFCs” OR “VOCs” OR “industrial activity” OR “ammonia” OR “sulfur oxide/dioxide” OR “power plants” OR “landfills” OR “methane” OR “PFAS” OR “polycyclic aromatic hydrocarbon” OR “cadmium” OR “metalloestrogesn” OR “microplastic” OR “PbSe Nanoparticles”) AND (“Sperm” OR “Sperm quality” OR “Sperm count” OR “Sperm volume” OR “Sperm motility” OR “Sperm vitality” OR “Sperm antibodies” OR “Sperm pH” OR “Sperm viscosity” OR “Sperm morphology” OR “Sperm DNA” OR “sperm DNA fragmentation” OR “Sperm DNA integrity” OR “semen quality” OR “semen parameters””. Conference abstracts and reference lists of included articles were hand-searched to identify any potential additional relevant work.

Study selection

Following the PICOS (participants, intervention, controls, outcomes, study design) criteria, we included studies assessing the influence of pollutants (categorized as carbon Disulfide;

environment pollution; lead; occupational not specified; polycyclic aromatic hydrocarbons; smoking; traffic pollution) on sperm parameters in observational (case-control, cross-sectional, cohort) studies.

The WHO sperm parameters values were considered as reference values (Cooper 2010).

Studies were excluded if they included pediatric populations; if the data were not analyzable; in vitro studies; or if they did not clearly report data regarding sperm parameters. No language restriction was a priori applied.

Data extraction

For each eligible study, two independent investigators (MT, DP) extracted: name of the first author and year of publication, setting, sample size, mean age of the population, mean body mass index (BMI), sperm parameters, type of pollutant. Data about matching and method (i.e. propensity score) were planned to be extracted between exposed and controls, but no study included this information.

Outcomes

The primary outcomes considered regarded sperm parameters investigated as sperm count, volume, concentration, motility, vitality, morphology, DNA fragmentation and chromatin damage. All parameters were reported in the original papers as mean with standard deviations (SDs); if they were reported differently, we transformed them into mean±SD.

Assessment of study quality

Two independent authors (MT, LS) carried out the quality assessment of included studies' using the Newcastle-Ottawa Scale (NOS) (Wells 2020). The NOS assigns a maximum of 9 points based on three quality parameters: selection, comparability, and outcome (Luchini 2017).

Data synthesis and statistical analysis

All analyses were performed using Stata, version 15.0. For all analyses, a p-value less than 0.05 was considered statistically significant.

The primary analysis compared the values of sperm parameters between high exposure to the pollu-tant and low exposure or none. We calculated the difference between the means of the groups, using the standardized mean differences (SMD) with their 95% confidence intervals (CIs), applying a random-effect model, since a clinical heterogeneity in terms of participants was hypothesized (Higgins 2008).

Heterogeneity across studies was assessed by the I^2 metric. Given significant heterogeneity (I^2 $\geq$50% and/or p<0.05) (Higgins 2011) and having at least 10 studies for each outcome, we planned to run meta-regression analyses, including factors cited in the data extraction paragraph as moderators. However, no outcome included 10 studies and so these analyses were not possible.

Publication bias was assessed by visual inspection of funnel plots and using the Egger bias test (Egger 1997). In case of publication bias, when ≥ 3 studies were available, we used the Duval and Tweedie non-parametric trim-and-fill method to account for potential publication bias (Duval 2000). Based on the assumption that the effect sizes of all the studies are normally distributed around the center of a funnel plot, in the event of asymmetries, this procedure adjusts for the potential effect of unpublished (trimmed) studies (Egger 1997). However, no outcome was determined to have publication bias.

RESULTS

Literature search

As shown in **Figure 1**, 1,182 articles were initially screened and 120 full texts were retrieved. Among them, 22 (Al-Bader 1999; Ghaffari2012; Bergamo 2016; Boggia 2009; Calogero 2011; Cannarella 2019; De Rosa 2003; Guan 2020; Guo 2016; Given 2008; Jeng 2014; jenny 2016; Kasperczyk 2008; Kumosani 2008; Ma 2010; Meyer 1981; Omu1998; Poli 2020; Sergerie 2000; Vanhoorne 1994;Wijesekara 2015; Zhou 2014) studies were finally included.

Descriptive findings and quality assessment

Table 1 reports the most important findings of the 22 studies included, with the majority of studies carried out in Asia (n=13). Overall, 4460 participants (range: 34-1346) were included having a mean age of 30.8±6.8 years (range: 28.9-37.9).

The median quality of the studies was 5.29 (range: 4-7), indicating an overall good quality of the studies, according to the NOS.

Influence of pollutants on sperm parameters

Table 2 and Figures 2 and 3 report aggregated findings by type of pollutant comparing sperm parameters between the “high exposure” and “low exposure or none” groups.

High exposure to pollution was found to have a negative impact on semen volume (n=13 studies; 2098 participants; SMD= -0.28; 95%CI: -0.37 to -0.20; p <0.0001; I^2=91.3%). In particular, semen volume was significantly reduced by specific pollutants such as smoking, traffic pollution and carbon disulphide). Similarly, pollutants negatively affected sperm count (n= 11 studies; 1743 participants; SMD=-0.42; 95% CI: -0.52 to -0.32; p<0.0001; I^2=96.2%). Also a greater exposure to tobacco smoking, traffic pollution, carbon disulphide, polycyclic aromatic pollutants was associated with lower sperm count (full details in **Table 2**). Pollutants had a negative impact on sperm concentration (n=16 studies; 2365 participants; SMD=-0.25; 95%CI: -0.33 to -0.16; p<0.0001; I^2=88.6%), on sperm vitality (n=4 studies; 533 participants; SMD= -0.78; 95%CI: -0.96 to -0.59; p <0.0001; I^2=94.7%), on sperm motility (n= 16 studies; 2339 participants SMD= -0.53; 95%CI: -0.62 to -0.43; p <0.0001; I^2=98.3%), sperm DNA fragmentation (n=3 studies; 199 participants; SMD=1.08; 95%CI: 0.73- 1.44; p< <0.0001; I^2=97.8%) and chromatin damage (n=3 studies; 325 participants; SMD=1.80; 95%CI: 1.51 to 2.09; p <0.0001; I^2=98.3).

No aggregated data suffered on publication bias at the funnel plot inspection and having a p-value >0.05 at the Egger’s test (data not shown).

DISCUSSION

The present meta-analysis found that environmental and occupational pollutants may affect sperm quality. All included articles reported significant alterations in at least one of the outcomes evaluated in association with at least one of the pollutants studied. Sperm volume and total count were evaluated in 13 and 11 included studies, respectively. Both parameters were significantly negatively associated to smoking, carbon disulphide and traffic pollution. Traffic pollution included generally gaseous pollutants as nitrogen oxides, sulphur compounds and sulphur oxides. Sperm total count was also affected by polycyclic aromatic. Nevertheless, both parameters were not significantly affected by lead exposure and environment pollution. The latter included sulfur dioxide, nitric dioxide, nitric oxides, carbon monoxide, ozone, methane, non-methanic hydrocarbons and volatile organic compounds. Recent evidence reported that an increasing exposure to endocrine disruptors is associated with decreased semen volume (Zamkowska 2018). Sperm concentration, intended as the ratio of total spermatozoa to volume, resulted significantly negatively associated only in the 4 studies on traffic pollution exposure. This probably reflects a drastic reduction of the count in cases exposed to pollutants rather than a normal condition in non-exposed subjects. Vitality was assessed only in 4 studies and, among these, only carbon disulphide exposure was found to affect this parameter. Sperm motility was studied in 16 of the included studies and was found to be impaired in all except environmental and polycyclic aromatic exposure. This parameter is of paramount importance to assess the quality of sperm and in terms of fertility. Sperm morphology was studied in twelve of the articles reviewed and was found significantly and negatively associated with traffic pollution, carbon disulphide polycyclic aromatic and lead exposure. Although the clinical relevance of this parameter is still debated, it seems relevant for in vitro fertilisation (Zinaman 2000).

Despite the increasing interest in DNA integrity, only 6 studies, 3 assessing the DNA fragmentation and 3 the chromatin damage, were included. Only polycyclic aromatic exposure did not significantly affect this parameter.

In general, as expected, the exposure to pollutant agents is a risk factor for the impairment of sperm quality. Although the pathophysiology is not fully understood, at least two mechanisms could be hypothesised to explain this association. First, a direct action of toxic pollutants on spermatozoa may explain a lower quality of sperm. There is growing evidence utilising in vitro studies to suggest this direct toxicity likely acting through the alteration of plasma membrane fluidity and electrochemical potential (Sabovic 2020). Another interesting reported mechanism, causing mainly motility impairment, is the activation of the apoptotic cascade in spermatozoa that can result in the loss of motility (Aitken 2015). Pollutants may also act negatively on sperm motility by altering mitochondrial function and up-regulating pro-apoptotic genes at the mitochondrial level (Sipinen 2010). Finally, chemical agents may have a negative effect on sperm parameters acting as endocrine disruptors.

Sperm DNA damage mechanisms are currently unclear. It has been suggested that the damage occurs by means of substances produced by unknown pathways of pollutants metabolism (Sipinen 2010). Finally, pollutants have been found to increase oxidative stress by increasing reactive oxygen species production resulting in increased lipid peroxidation, caspase and endonuclease activation (Sipinen 2010; Hughes 2009).

Although in vitro studies allow to verify some hypothesis on effects and mechanism of pollutants, they have the following some important limitations for in vivo considerations: i) in in-vitro studies, it is possible to exactly know the exposure concentration while it is unknown the effect of the human exposure on reproductive system; ii) in vivo, the harmful effects of pollutants are the result of a chronic exposure; iii) in vivo, there is a simultaneous exposure to several pollutants that may interact and increase toxicity.

In addition to the direct toxicity, the reduction of sperm quality may be the result of an alteration of the testis or of the reproductive tract function. A growing body of evidence suggests a role of pollutants as endocrine disruptors leading to genital disorders (impaired spermatogenesis and reproductive defects) and antiandrogenic-driven conditions (testicular dysgenesis syndrome) (Skakkebaek 2001; Acerini2009). Interestingly, also in utero exposure to pollutants seems to be associated to lower sperm quality and higher levels of LH and FSH at adulthood (Vested 2013). Moreover, some pollutants have an estrogenic or an anti-androgenic action, affecting the downstream signalling pathways of sex hormones, down-regulating the hypothalamic-pituitary axis activity and increasing the testicular toxicity (Kjeldsen 2013; Jensen 2008). Finally, growing concern is caused by the possible impact of climate change on fertility (Walsh 2019). In fact, the extreme temperatures derived form the climate change may lead to the loss of fertility not only for humans but for all animals and plants (Walsh 2019).

Findings from this meta-analyses must be considered in light of its limitations: i) in relation to environment pollutants there is no standard method to test levels in different tissues; ii) it is not possible to assess the effects of simultaneous exposure to several pollutants; iii) despite the clear negative impact on sperm, the exact pathophysiological mechanisms are not fully understood.

In conclusion, considering the increasing attention paid to climate change and environment health, this work may be considered a milestone for future studies regarding male fertility. Moreover, sperm quality can be considered a proxy for general health and, thus, this evidence open a multidisciplinary stream including andrology, endocrinology, gynaecology, genetic, embryology and public health. It would be strongly recommended to increase and improve efforts in order to better understand the role that pollutants play on human, animal and planetary health and to draft policies to defend our future.

Author contribution

Conceptualisation, D.P. and A.G.; Methodology, J.D.; Formal Analysis, C.F.; Data Extraction, D.P and M.T.; Writing – Original Draft Preparation, A.B., D.P., A.G.; Writing – Review & Editing, C.V., L.S.; Supervision, L.S.

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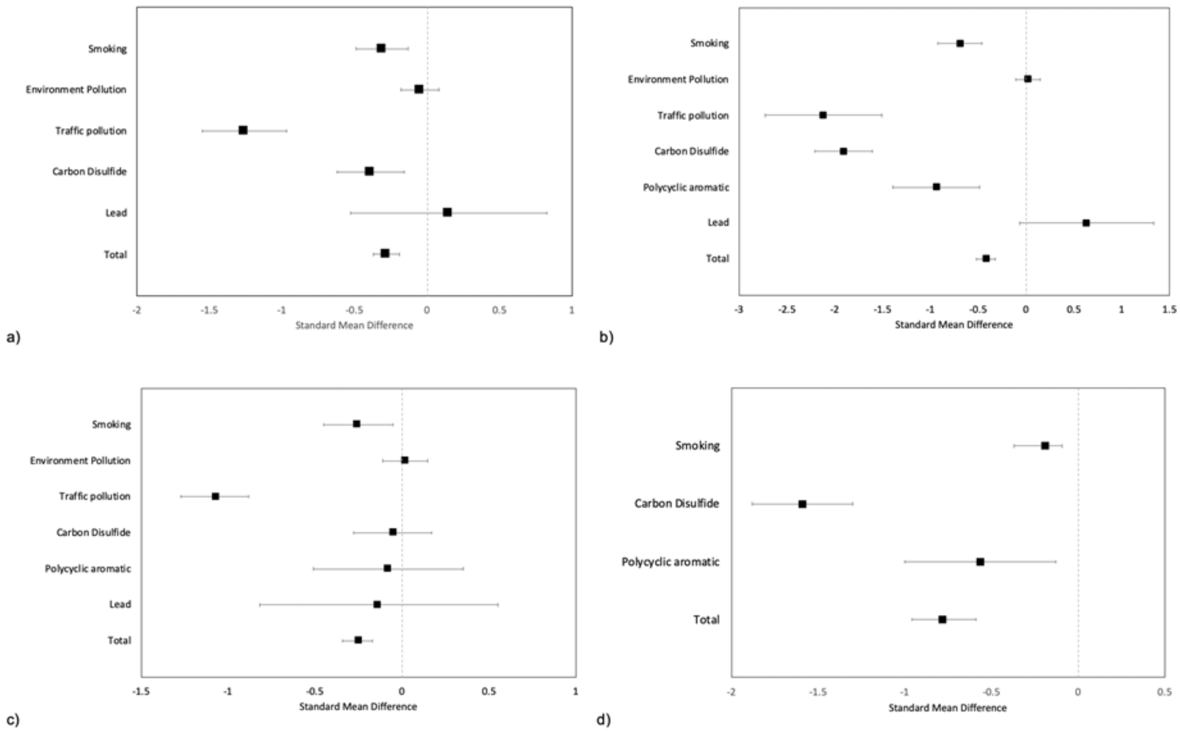
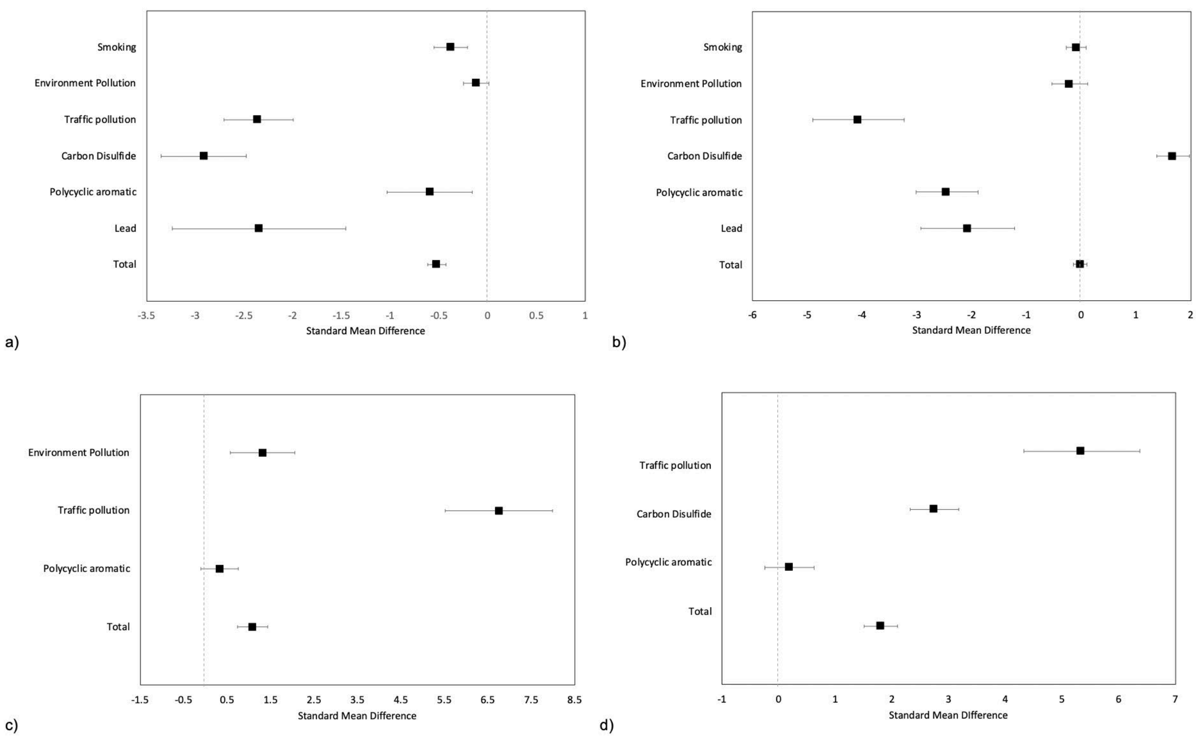
Legend to figure

Figure 1. PRISMA flow chart.

Figure 2. Aggregated findings by type of pollutant comparing a) sperm volume b) sperm count c) sperm concentration, and d) sperm vitality between the “high exposure” and “low exposure or none” groups.

Figure 3. Aggregated findings by type of pollutant comparing a) sperm motility b) sperm morphology c) sperm DNA fragmentation, and d) chromatine damagebetween the “high exposure” and “low exposure or none” groups.

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