

## Air Pollution and Quality of Sperm: A Meta-Analysis

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**Context:** Air pollution is common in all countries and affects reproductive functions in men and women. It particularly impacts sperm parameters in men. This meta-analysis aimed to examine the impact of air pollution on the quality of sperm.

**Evidence Acquisition:** The scientific databases of Medline, PubMed, Scopus, Google scholar, Cochrane Library, and Elsevier were searched to identify relevant articles published between 1978 to 2013. In the first step, 76 articles were selected. These studies were ecological correlation, cohort, retrospective, cross-sectional, and case control ones that were found through electronic and hand search of references about air pollution and male infertility. The outcome measurement was the change in sperm parameters. A total of 11 articles were ultimately included in a meta-analysis to examine the impact of air pollution on sperm parameters. The authors applied meta-analysis sheets from Cochrane library, then data extraction, including mean and standard deviation of sperm parameters were calculated and finally their confidence interval (CI) were compared to CI of standard parameters.

**Results:** The CI for pooled means were as follows:  $2.68 \pm 0.32$  for ejaculation volume (mL),  $62.1 \pm 15.88$  for sperm concentration (million per milliliter),  $39.4 \pm 5.52$  for sperm motility (%),  $23.91 \pm 13.43$  for sperm morphology (%) and  $49.53 \pm 11.08$  for sperm count.

**Conclusions:** The results of this meta-analysis showed that air pollution reduces sperm motility, but has no impact on the other sperm parameters of spermogram.

**Keywords:** Male Infertility; Air Pollution; Sperm

### 1. Context

The incidence of infertility has been increasing in industrial countries from 7% - 8% in 1960 to 20% - 35% nowadays (1). Decreasing infertility rate is a top priority for the World Health Organization (2). Over the past 50 years, human sperm concentration decreased drastically from 113 to 61 million/mL, which represents almost 50% decrease (3). Evidence showed that human semen quality and fecundity have been also declining during the last decades, in particular in the United States and Europe (2-4). For example it has been estimated that the sperm count in American males is decreasing by 1.5% each year (5, 6). In Iran, during the last 20 years, the infertility rate has been increased. One-fourth of Iranian couples are infertile, which means that three-fourth will be infertile by the end of their reproductive age. Also infertility rate within Iranian men has been increased by 20% and the primary infertility rate has been increased two fold during the recent two decades (7). These dramatic changes in fertility are very important

and should be treated with great caution (1). Moreover, the continuous increase in infertility rate and testicular cancer as well as reduction in sexual relationships has created serious concerns in relation to human reproduction during recent years (1).

On the other hand, the effect of geographical variations in semen quality (8, 9) and other changes in men reproductive functions, support the idea that specific factors, present in some areas but not in others, may be responsible for the decline in semen quality (4, 5). Environmental and life style factors have been explored as possible contributors to these changes, in particular, continuous exposure to environmental endocrine disrupting chemicals has been implicated (6). It has been reported that the male reproductive system malfunction seems to be a good sensitive marker of environmental hazards (4). Alteration of the male reproductive system may result from gonadal endocrine disruption or by direct damage to the spermatogenesis (6). Epide-

miological studies provided equivocal results concerning the effects of lead (Pb) and cadmium (Cd) elements on hormone concentration, male infertility, and sperm parameters. Geographic differences in the amount of naturally occurring Cd have been correlated with the rate of prostate cancer (8-10). More recent studies conducted in the United States have also reported the association of ambient air pollution (but for individual pollutants) with sperm quality (9). Exposure to air pollution has been linked to alterations in sperm parameters. Air pollution is usually associated with increased air content of carbon monoxide (CO), nitrous dioxide (NO<sub>2</sub>), sulfur dioxide (SO<sub>2</sub>), ozone, lead (Pb), and particulate matter. Particulate Matter (PM) in the respirable range (PM 2.5) is of particular interest, because it can carry multiple trace elements and Polycyclic Aromatic Hydrocarbons (PAHs), a group of compounds that include several endocrine disruptors. It is worth to mention that endocrine disruptors can affect both the hypothalamic-pituitary axis and testicular spermatogenesis and have the potential for causing sperm alterations (2, 6, 11, 12). Additionally, some studies have suggested that environmental toxins alter sperm DNA integrity (9).

Nowadays, owing to the changes in population pattern, decrease in fertility rate, change in life style, and the continuous increase in the diagnosis and treatment expenses, it is very important to find the exact causes of infertility. Therefore, performing a meta-analysis, which can answer the question of "Does air pollution affect male infertility?" becomes of great interest and priority, for both scientists and governmental institutions. The answer to this question can change the attitude of infertile men who live in cities with high air pollution. Also, the results can provide fruitful and precious information to the guardians of the environment to develop practical solutions to remove contaminants harmful to the sperm parameters.

The purpose of this meta-analysis was to answer these two questions: 1) can air pollution change the quality parameters of sperm such as semen volume, sperm count, sperm morphology, and motility? and 2) can air pollution be considered a factor to cause infertility in men?

## 2. Evidence Acquisition

### 2.1. Data Sources

In this meta-analysis, articles were included with the subjects related to the impact of air pollutants on male infertility published between 1978 and 2013. The year 1978 was chosen because Dama *et al.* in their study showed that for more than 30 years, the sperm quality in some parts of the world has been changed and accordingly, a new attitude for infertility in men has been developed (13). While most meta-analyses focus on relationships between variables, some have the goal of

estimating a mean, risk, or rate in a single population. For example, a meta-analysis might be used to combine several estimates for the prevalence of Lyme disease in Wabash County or the mean SAT score for students in Utah. In these cases, the index is clearly neither a treatment effect, nor an effect size, since effect implies a relationship. Rather, the parameter being estimated could be simply called a note; however, that the classification of an index as an effect size and or a treatment effect (or simply a single group summary) has no bearing on the computations.

In the meta-analysis itself, we have simply a series of values and their variances, and the same mathematical formulas apply Single-group summary (14). However, all included articles were those in which involved men (1) were settled in polluted cities (2), did not have any occupation risk factor, and (3) had no history of cigarette smoking and alcohol consumption as well as drug addiction. All selected articles were in English apart from two articles, one Chinese and another one in Polish, where the authors contacted these two papers' corresponding authors and requested original papers in English, but received no reply so that they were included by abstract. The review articles, letters to the editor, and articles in newspapers were excluded. Also only the articles were included that reported the relative risk, confidence interval, and odds Ratio. PubMed, Medline Plus, Google scholar, Cochrane Library, ProQuest, Scopus, and Ovid were databases, which were searched. If the original article was not accessible from the Mashhad University of Medical Sciences, we tried to get it from private institutes inside Iran or through University Putra Malaysia.

### 2.2. Study Selection

The ecological correlation studies, cohort, case control, and cross-sectional studies were found through electronic and hand searching of retrieved articles' references. The search carried out in the time period between January 1978 and November 2013. Key words included 'male infertility,' 'air pollution,' 'non-exposure infertility,' and 'reproductive disorder,' which searched with "and". All papers were downloaded to Mendeley software to be stored and analyzed. Databases search resulted in 59 papers. Seventeenth papers were also found through hand searching of the retrieved electronic references (76 papers in total). The abstracts and papers in conferences did not include in the study. Out of the 76 original articles, 41 articles were excluded during the initial screening. Of these, 19 articles evaluated the effect of wireless waves, mobile phones, Wi-Fi, six occupational pollutant, four articles focused on male infertility due to heart diseases and surgery such as varicocele, and 12 articles assessed the therapeutic success of in vitro fertilization IVF in men who had been exposed to contaminants. Six articles were either systematic or conventional review. The remaining 35 articles

were scrutinized due to these reasons: 8 articles because of the lack of clear research process, 4 ones owing to the low sample size of the pilot study, and the rest for failing to provide accurate statistics. Finally, 11 articles were included in this meta-analysis. On the one hand, the included articles were few and on the other hand, mean and SD indexes were not mentioned for people who exposed to air pollution in all articles, therefore the method of analysis had been done by one group. First, pooled index had been calculated in exposed group by DerSimonian and Laird random method then provided forest plot and finally they compared one by one with standard rate of sperm quality.

### 2.3. Data Extraction

In order to extract the data, first a trained person extracted the data from data set and statistical tables prepared by the statistical expert. Then, all data were checked by the first author and eventually hit by another consultant who reviewed and analyzed the data by "Stata" data analysis software.

## 3. Results

### 3.1. Statistical Analysis

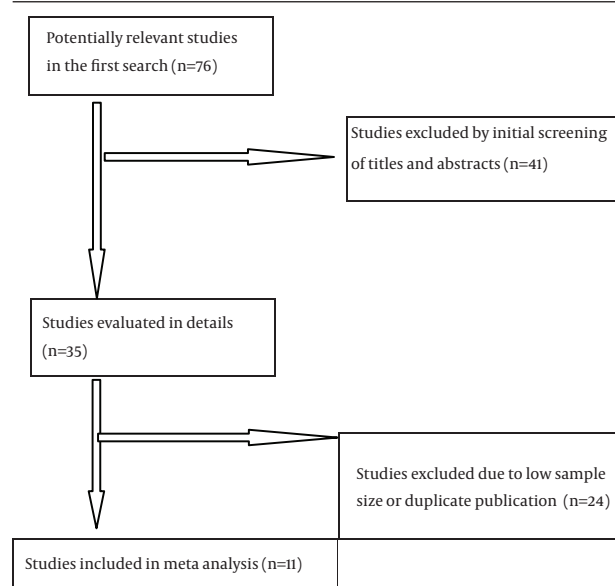
Statistical analysis was performed using Stata software version 11. For the heterogeneity of studies, Cochran's Q test at a significance level of 0.1 was used. To demonstrate the heterogeneity, index I<sup>2</sup> was used. Forest plots were used for the detection of mean pooling. Because of heterogeneous nature of the studies on the impact of air pollution on the quality of sperm, random effects model (DerSimonian and Laird method) was used for data pooling. Out of 55 articles published in scholarly journals (which were found in various stages of search), 11 papers with relevant research topics were selected. The other articles were excluded for reasons such as failing to report the number of variables and using different measuring criteria (Figure 1). Among these 11 articles, the mean volume of ejaculated sperm in 7 articles, the mean concentration of sperm in 4 articles, the mean of sperm motility in 7 articles, the mean of sperm morphology in 5 articles, and the mean sperm count with standard deviation or standard error in 7 articles were reported. The total number of samples included in this meta-analysis was 2945 (Table 1).

Among the eligible studies, the highest ejaculation volume was reported by EL-Zohairy *et al.* (1996) (15) as  $3.4 \pm 0.1$  mL and the lowest mean was reported by Rubes *et al.* (2007) (16) as  $1.96 \pm 0.13$  mL. Cochran test demonstrated heterogeneity between studies ( $P < 0.001$ ,  $I^2 = 0.98$ ). The mean integration using DerSimonian and Laird random effects model (3-2.35) was 2.68 (2.35-3) (Table 2, Figure 2). Among the eligible studies the highest sperm concentration was reported by Sokol *et al.*

(2005) (17) as  $87.5 \pm 0.02$  million per milliliter and the lowest value by Jouannet *et al.* (2001) (18) as  $39.6 \pm 0.03$  million per milliliter. Cochran test showed heterogeneity between studies ( $P < 0.001$ ,  $I^2 = 0.99$ ). The mean integration using the DerSimonian and Laird random effects model was 62.1 (77.98 to 46.22) (Table 2) (Figure 3). Among the eligible studies, the highest motility was reported by Xu *et al.* (2012) (19) as  $63.06 \pm 3.88$  and the minimum value by the Giaccio *et al.* (2012) (20) as  $25.7 \pm 1.45$  (%). Cochran test indicated heterogeneity between studies ( $P < 0.001$ ,  $I^2 = 0.98$ ). The mean integration using the DerSimonian and Laird random effects model was 39.4 (33.88 to 44.92) (Table 2, Figure 4). Among studies which reported the morphology, the highest belonged to EL-Zohairy *et al.* (1996) (15) as  $42.14 \pm 1.12$  (%) and the minimum value was reported by Selevan (2000), as  $13.2 \pm 1.86$  (%). Cochran test indicated heterogeneity between studies ( $P < 0.001$ ,  $I^2 = 0.99$ ). The mean integration using the DerSimonian and Laird random effects model was 23.91 (37.34 to 10.48) (Table 2 and Figure 5). Among eligible studies the highest sperm count was recorded by Selevan *et al.* (2000) (14) as  $129.1 \pm 29.48$  million per milliliter and the minimum value by EL-Zohairy *et al.* (1996) (15) as  $1.14 \pm 1.25$  million per milliliter. Cochran test indicated heterogeneity between studies ( $P < 0.001$ ,  $I^2 = 0.99$ ). The mean integration using the DerSimonian and Laird random effects model was 49.53 (60.62 to 38.45) (Table 2 and Figure 6).

## 4. Discussion

This study examined the impact of air pollution on sperm parameters. The meta-analysis was conducted on 11 articles out of total 79 found articles. It showed that air pollution can lead to reduced sperm motility and



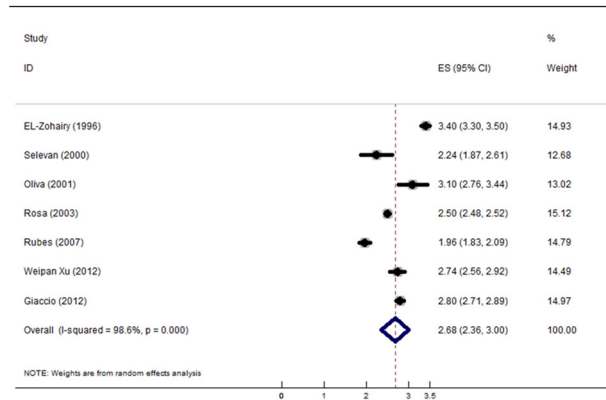
**Figure 1.** The Selection Process of Paper for This Meta-Analysis Study

**Table 1.** Characteristics of Sperm in the Included Studies

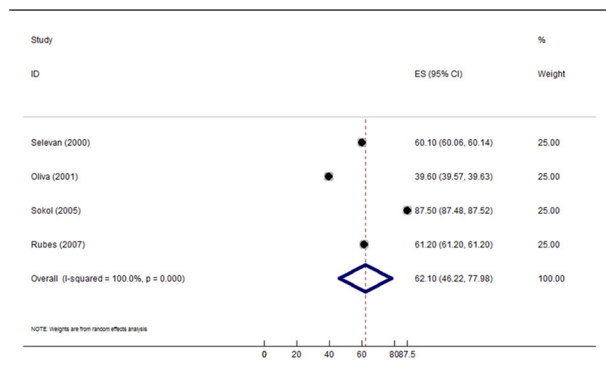
Authors	Publication year	Type of Study	Sample Size	Volume, mL	Concentration, Million per milliliter	Motility, %	Morphology, %	Count, million
Xu et al. (19)	2012	cross-sectional	96	2.74 ± 0.88	N/A	63.6 ± 19.4	16.6 ± 8.8	N/A
Selevan et al. (14)	2000	prospective	47	2.24 ± 1.28	60.1 ± 46.7	32.5 ± 13.2	13.2 ± 6.5	129.1 ± 103.1
Sokol et al. (17)	2005	prospective	48	N/A	87.5 ± 25	N/A	N/A	N/A
Jouannet et al. (18)	2001	prospective	67	3.1 ± 1.4	39.6 ± 63.3	41.7 ± 23.6	33.6 ± 14.9	N/A
Hansen et al. (21)	2010	prospective	228	N/A	N/A	N/A	14.1 ± 5.8	N/A
Singh et al. (10)	1998	retrospective	1425	N/A	N/A	N/A	N/A	53.23 ± 24.06
Giaccio et al. (20)	2012	cross-sectional	601	2.8 ± 1.1	N/A	25.7 ± 18.1	N/A	17.8 ± 16
Inhorn et al. (22)	2008	retrospective	76	N/A	N/A	46.45 ± 18.05	N/A	38.81 ± 25.91
De Rosa et al. (23)	2003	retrospective	85	2.5 ± 0.1	N/A	34.7 ± 2.2	N/A	32.4 ± 2.4
Rubes et al. (16)	2007	prospective	272	1.96 ± 1.06	61.2 ± 60.09	N/A	N/A	113.3 ± 119.2

**Table 2.** Mean Pooling for Sperm Parameters and Their %95CI Based on Meta-Analysis

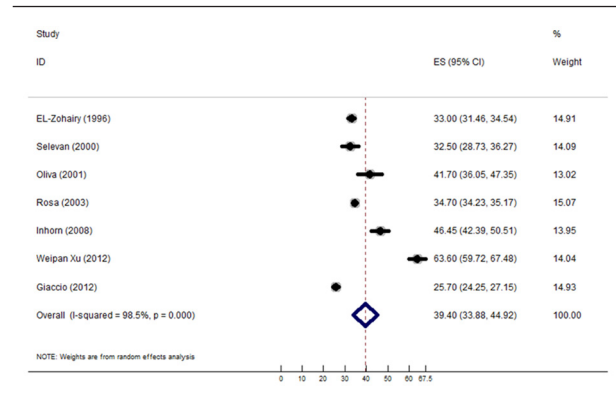
Index	Sample Size	No. of Studies	Mean	95%CI
Ejaculation volume, mL	1223	7	2.68	(2.36-3)
Sperm Concentration, Million per milliliter	434	4	62.1	(46.22-77.98)
Sperm Motility, %	1027	7	39.4	(33.88- 44.92)
Sperm Morphology, %	493	5	23.91	(10.48- 37.34)
Sperm Count, million	2561	7	49.53	(38.45-60.62)



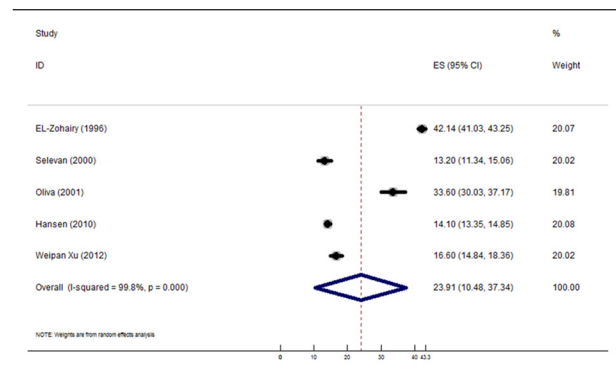
**Figure 2.** Forest Plot of the Mean Pooling for Ejaculation Volume



**Figure 3.** Forest Plot of the Mean Pooling for Sperm Concentration

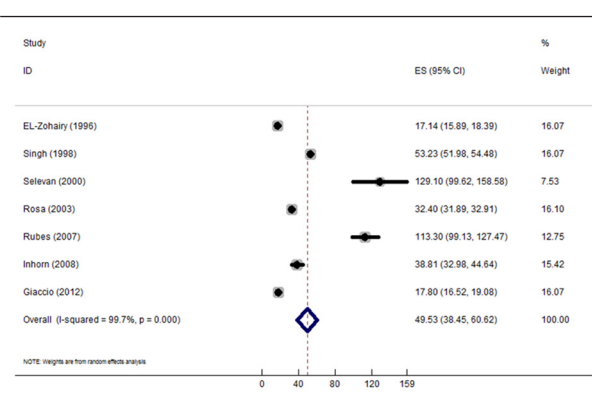


**Figure 4.** Forest Plot of the Mean Pooling for Sperm Motility



**Figure 5.** Forest Plot of the Mean Pooling for Sperm Morphology





**Figure 6.** Forest Plot of the Mean Pooling for Sperm Count

amongst the concentration, morphology, and semen volume parameters, sperm motility is more affected by the air pollution (6, 14, 18, 24-26). Hammoud (2009) and Guven (2008) showed that sperm motility and sperm count would reduce in men living in the polluted cities (6, 25). Li and colleagues showed that a high proportion of Chinese healthy males (61.1%) had abnormal semen parameters values, according to WHO criteria, compared to the values reported by studies carried out in the USA and Europe for the mean of semen volume and sperm total motility (26). It should be noted that some studies, which investigated the effect of certain pollutants were excluded from this study due to small sample size. Authors only studied the papers, which generally examined the effect of air pollutants (other than wireless signals, Wi-Fi, and mobile phone) on sperm parameters. It is noteworthy that the authors of this article attempt to do another review about the effect of the waves on the sperm parameters.

During the last 30 to 50 years, some changes in sperm parameters have been reported in different places of the world (4, 27, 28). Several factors have contributed in this change. Evidence has shown that the most important ones include changes in lifestyle and environmental factors (2, 7, 29). In a meta-analysis done by Carlsen et al. a reduction in sperm count has been reported in America and Northern Europe during the last 50 years (29). Several studies have shown that the reason of at least half of male infertility cases is unknown, and it seems that environmental factors and pollutants can have a role in its etiology (30, 31). Air pollutants, compounds of lead, cadmium, and mercury can damage the male reproductive system. Pollutants may impair or disrupt the spermatogenesis and affect HPO axis as well as making change in the level of LH and FSH, which result in changes in sperm parameters. Recent studies have shown that the target of pollution is DNA fragmentation in sperm (31). Heavy metals such as lead, mercury, and cadmium in air pollutants also reduce the sperm motility and sperm morphology and are associated with changes in the sperm DNA (31, 32).

If the age of exposure to pollution was lower, damage

will be longer and will cause a higher potential risk (26, 32). However, Rubes et al. showed that short-term exposure to pollutants causes serious damages in men and women's reproductive system (16). De Rosa et al. showed that young and middle-aged men are more affected by air pollution and the possibility of damage to sperm in this age will be higher (23). Hammoud et al. showed that 2 to 3 months exposure to air pollution decreases motility levels ( $P = 0.044$ ) (6). Although nowadays assessment of sperm motility is not the only test used for the assessment of male infertility, it is the first step of infertility evaluation (23). Half of the cases of male infertility are due to decreased sperm motility and low sperm count, which has a higher rate in developing countries (23). The mechanisms through which pollutants affect men's infertility are not clear yet, but as pollutants are capable to accumulate in body fluids such as blood, urine, and seminal fluid, it may affect HPO axis or DNA fragmentation in sperm. However, there are many studies that have shown positive significant DNA fragmentation and air pollution but the exact mechanism is not clearly known.

However, some have suggested that air pollution can alter sperm DNA integrity (33, 34). Although Telisman et al. showed that even small amounts of contaminants such as lead, cadmium, mercury, and copper can alter sperm quality parameters ( $P < 0.0001$ ), no decisive influence of these agents have been reported on the reproductive endocrine system (35). In different studies, various results have been reported about the effects of air pollutants on sperm parameters. Xu et al. in an extensive cross-sectional study demonstrated that air pollutants can affect sperm parameters in men living in Chongqing, China. Also they compared sperm parameters (motility, concentration, and morphology) in people who exposed to air pollutants with people who had cigarette smoking and alcohol consumption, final results showed that air pollution can produce changes in sperm parameters ( $P = 0.02$ ) (19). Selevan et al. in their study stated that in the young men exposed to air pollutants, sperm motility, and sperm morphology show transient changes but more changes are seen in sperm chromatin, however no difference is observed in sperm count (14). This meta-analysis showed that although sperm motility has changed, sperm count has not.

Another impact of air pollution on sperm is increasing DNA fragmentation that has been reported in some studies such as Sokol et al. (2006) (17) who investigated the effect of air pollutants and ozone on sperm quality. They reported that pollutants have no effect on sperm quality; however, ozone could make changes in sperm quality via oxidative stress. The oxidative stress can lead to the fragmentation of sperm, affecting its function and as a result decreasing fertility (6, 17, 23). Hansen et al. conducted a cohort study in which they found that the air pollutants and ozone have statistically significant correlation with the changes in the sperm quality (21). Also changes in motility of the sperm has been reported in a traffic guide po-

liceman who worked in the crowded parts of Los Angeles (10). Inhorn et al. (22) showed that occupational and environmental contaminants were associated with two-fold increase in the risk of infertility but heavy metals had no impact on sperm quality of Lebanese men (30). It is notable that they did not distinguish between air pollution and exposure to occupational pollution in spite of increasing two-fold male infertility which had been caused by heavy metals level in blood. Comhaire et al. (30) have shown that air pollution has effect on sperm motility, but with removing contamination it will return to the normal level (20, 33).

Amongst the air pollutants, lead has the greatest risk for quality of sperm and spermatogenesis, as De Rosa et al. (23) showed that lead is a major air pollutant that causes serious damage to the spermatogenesis as well as semen parameters. On the other hand, some studies have not found any association between air pollution and increased male infertility rate. In this regard, El-Zohairy et al. (15) showed that although the average level of lead in sperm of Egyptian men is higher than the Europeans, their infertility rate is not higher. Therefore, the association between fertility and air pollution is not clear and other relevant factors should be considered. Obviously, the cause of male infertility is not just disturbed sperm motility or sperm parameters, and the other factors such as geographic areas, life style, and seasons also affect quality of sperm, as El-Zohairy has pointed to them (15).

In conclusion, the results presented in this meta-analysis are based on 11 papers. The authors confronted some limitations such as difficulty in accessing the databases, lack of clinical studies in the explored subject, and limitation of epidemiological evidence about the impact of environmental pollutants on reproductive functions. Furthermore, there were some uncertainties in the articles. For instance, in some studies, the research process was not clear. In some, the effect of heavy metals or gaseous pollutants such as ozone was just reported. Besides, the duration of exposure to pollution was not mentioned in any study. So this meta-analysis could just investigate the pollutants' effect on sperm parameters. The strength of our study was inclusion of all studies conducted from 1974 up to now, focused on the explored topic. In this time period, numerous studies investigated the effects of environmental factors on male reproductive function and gradually a novel relationship was found between male infertility and air pollution. The present study also clearly answered the first question of this study so it seems that concerns about declining male fertility in metropolitan areas may resolve. The authors recommend future studies to examine the relationship between duration and intensity of exposure to contaminants with severity of male infertility; as it can provide an answer for the second research question in this study. In addition, it is recommended to consider the effect of air pollutants on DNA fragmentation of sperm. Although the results of this study showed that sperm motility decreases by exposure

to air pollution, this factor alone cannot justify the drastic changes in the rate of infertility in polluted cities. The authors recommend using markers such as DNA fragmentation in men with low fertility or sperm parameters that live in the pollutant areas. The results of this meta-analysis showed that air pollution can reduce sperm motility without changing the other parameters.

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## Authors' Contributions

Tahereh Fathi Najafi was the main investigator and wrote the article. Dr Robab Latifnejad Roudsari contributed to the study design, interpretation of data and revision of the manuscript critically for important intellectual content. Dr Farideh Namvar revised and analysis some articles. Dr Vahid Ghavami did the statistical process. Zahra Hadizadeh Talasaz and Mahin Esmaeli contributed to the data extraction.

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