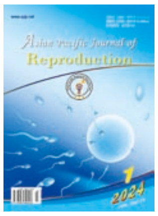


Meta-Analysis

Asian Pacific Journal of Reproduction

Journal homepage: www.apjr.net

doi: 10.4103/apjr.apjr_95_23

Exploring the relationship between ambient sulfur dioxide and semen quality parameters: A systematic review and meta−analysis

Seyed Sobhan Bahreiny[1,2✉], Mojtaba Aghaei[1], Mohammad Reza Dabbagh[3], Hamid Ghorbani[1], Moslem Javidan[4], Reza Mohammadpour Fard[1,4]

[1]*Student Research Committee, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran*

[2]*Medical Basic Sciences Research Institute, Physiology Research Center, Department of Physiology, School of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran*

[3]*Department of Biology, Faculty of Science, Shahid Chamran University of Ahvaz, Ahvaz, Iran*

[4]*Department of Immunology, Faculty of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran*

ABSTRACT

Objective: To investigate the relationship between ambient sulfur dioxide (SO_2) exposure and semen quality parameters.

Methods: A systematic literature search was conducted to identify relevant studies investigating the association between SO_2 exposure and semen quality parameters. This search encompassed the timeframe from January 2000 to May 2023 and included electronic databases such as Web of Science, Google Scholar, PubMed, Cochrane, and Scopus. Pooled effect estimates with 95% confidence intervals (*CI*) were calculated using percent changes (PC). The meta-analysis included seven studies with 6 711 participants and 15 087 semen samples.

Results: The results revealed a significant negative association between ambient SO_2 exposure and certain semen quality parameters. In particular, SO_2 exposure was associated with a significant decrease in progressive motility (PC=0.032; 95% *CI*: -0.063 to -0.001; *P*=0.044) and sperm concentration (PC = -0.020; 95% *CI*: -0.036 to -0.005; *P*=0.012). However, no statistically significant associations were observed for total sperm count (PC = -0.038; 95% *CI*: -0.079 to 0.003; *P*=0.070), seminal fluid volume (PC = -0.009; 95% *CI*: -0.048 to -0.030; *P*=0.662) and sperm motility (PC = -0.17; 95% *CI*: -0.363 to 0.022; *P*=0.830). In addition, the results of the subgroup analysis revealed specific variables that were associated with the decrease in relevant sperm parameters.

Conclusions: This systematic review and meta-analysis provides compelling evidence supporting a consistent negative association between exposure to ambient SO_2 and semen quality parameters.

KEYWORDS: Semen quality; Sulfur dioxide; Ambient air pollution; Meta-analysis

1. Introduction

In our modern era, environmental pollutants pose a growing threat to human health[1]. Among these pollutants, sulfur dioxide (SO_2) stands out as a concerning and pervasive compound[2,3]. SO_2 is released into the atmosphere by industrial processes and fossil fuel combustion and has long been considered a significant contributor to air pollution and respiratory illness[4,5]. However, recent findings suggest that the effects of SO_2 extend far beyond the respiratory system, potentially affecting male reproductive health.

This influence is observed through its correlation with multiple semen quality parameters such as sperm concentration, motility, morphology, and DNA integrity[6]. It is crucial to comprehend the correlation between environmental SO_2 pollution and semen quality parameters to understand how environmental pollution affects human reproductive health[7]. By pooling data from multiple studies, we aim to discover potential associations and shed light on the complex interplay between environmental pollutants and male reproductive function[8]. The motivation behind this study is twofold. First, with increasing environmental SO_2 pollution from industry and urbanization, public health and reproductive medicine must investigate the effects on semen quality parameters[9]. Second,

✉To whom correspondance may be addressed. E-mail: bahreiny.s@ajums.ac.ir

This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-Share Alike 4.0 License, which allows others to remix, tweak and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

©2024 *Asian Pacific Journal of Reproduction* Produced by Wolters Kluwer- Medknow.

How to cite this article: Bahreiny SS, Aghaei M, Dabbagh MR, Ghorbani H, Javidan M, Fard RM. Exploring the relationship between ambient sulfur dioxide and semen quality parameters: A systematic review and meta-analysis. *Asian Pac J Reprod* 2024; 13(1): 12-21.

Article history: Received: 25 July 2023; Revision: 20 October 2023; Accepted: 12 November 2023; Available online: 26 January 2024

deciphering the relationship between SO_2 exposure and semen quality parameters can provide valuable insights into the underlying mechanisms by which environmental pollutants affect male fertility, paving the way for targeted interventions and prevention strategies. This meta-analysis aims to enhance the current comprehension of the correlation between exposure to environmental SO_2 and parameters related to sperm quality. The results not only augment the growing body of knowledge concerning the effects of environmental pollutants on male reproductive health but also may serve as the basis for future strategies and interventions to protect fertility in an increasingly polluted world.

2. Materials and methods

2.1. Protocol and registration

In order to ensure transparency and adhere to strict standards, this systematic review and meta-analysis study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyzes (PRISMA) guide. In addition, the study was registered in PROSPERO, a widely recognized database for registering systematic reviews[10] (CRD42023443428).

2.2. Eligibility criteria

The selection criteria for the studies included in this systematic review and meta-analysis were as follows: observational studies that investigated the association between exposure to ambient SO_2 and semen quality parameters, studies published between January 2000 and May 2023, and studies that provided data on semen quality parameters, including sperm concentration, motility, morphology, DNA integrity, and other relevant outcomes. The exclusion criteria comprised several elements, including studies that featured inappropriate comparators, inadequate study designs, or missing controls. Additionally, reviews, letters, editorials, animal studies, intervention studies, and conference proceedings were excluded. Finally, studies without extractable data were also not considered. The inclusion of these criteria was to ensure that the selected studies were of high quality and appropriate for the intended analysis.

2.3. Literature search

A comprehensive literature search was conducted in several electronic databases, including PubMed, Web of Science, Scopus, Cochrane, EMBASE, and Google Scholar. The search covered the period from January 2000 to May 2023. The search strategy used relevant keywords such as "ambient sulfur dioxide", " SO_2", " SO_2 exposure", "semen quality", "semen parameters", "semen", "spermatozoa", "spermatogenesis", "environmental pollution", "air pollution", "reproductive health", "male fertility" and related terms. The search strategy used relevant Boolean operators "AND" and "OR" to effectively combine keywords.

2.4. Study selection

Two authors SB & MJ conducted the initial search and evaluated the eligibility of studies based on predefined criteria. Any discrepancies were resolved by a third reviewer through consensus. The study selection process strictly adhered to the predefined inclusion and exclusion criteria.

2.5. Data extraction

A standardized data extraction form was developed to extract relevant information from the selected studies. This form was designed to adhere to the specific requirements of this meta-analysis, and a standardized checklist was explicitly created for this purpose[11,12]. The checklist captured essential information, including study details (first author, publication year, region), study design, participant characteristics (age, sample size), exposure assessment methods, measured semen quality parameters, and relevant statistical outcomes.

2.6. Quality assessment

The methodological quality and potential bias of the studies included in the analysis were assessed using the Newcastle-Ottawa scale, developed specifically for evaluating nonrandomized studies in meta-analyses. The Newcastle-Ottawa scale consists of three domains: selection of participants, comparability between groups, and assessment of outcomes or exposure. Based on the assigned scores, studies were classified as either low quality (score 4) or high quality (score 5), which allowed for a comprehensive assessment of their reliability and potential bias[13,14].

2.7. Statistical analysis

All statistical analyses were performed using Comprehensive Meta-Analysis (CMA) v3.7z software and IBM SPSS Statistics v26 software. All data collected from the included studies were analyzed using meta-analysis techniques. To evaluate the association between SO_2 exposure and semen quality parameters, the pooled percent changes (PC) ($[e^{\log\ scale\ \beta} - 1] \times 100$) were used along with the corresponding 95% confidence intervals (*CI*)[15,16]. This allowed quantification of the association per 10 $\mu g/m^3$ increase in SO_2 exposure. Statistical methods such as the I^2 statistic and Cochran's Q test were used to assess heterogeneity between studies. Heterogeneity was classified as low, moderate, or considerable with I^2 values of less than 30%, between 30% to 50%, and greater than 50%, respectively. In instances with substantial heterogeneity among studies, a random-effects model is employed. Conversely, when there is no significant

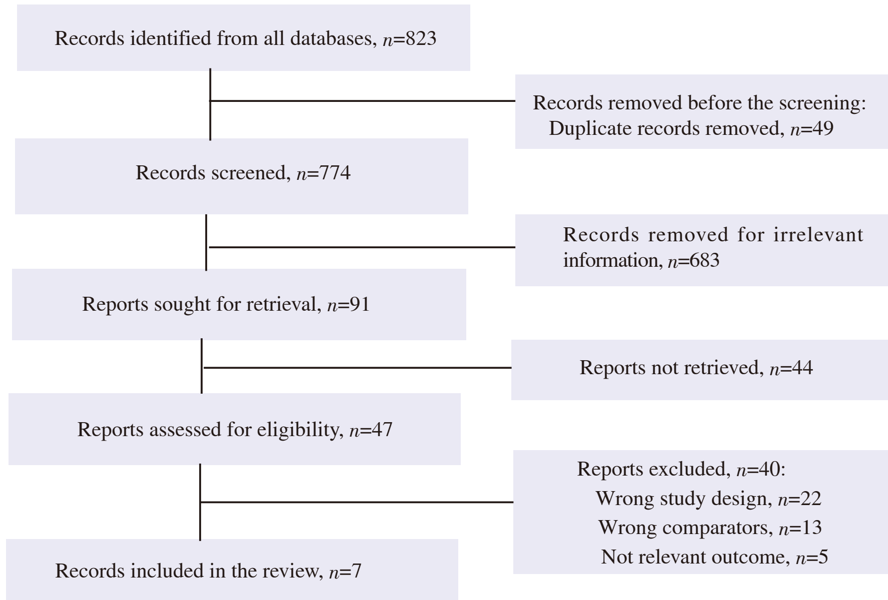


Figure 1. Flowchart of study selection.

heterogeneity, a fixed-effects model is applied for the meta-analysis. However, if heterogeneity was detected, we implemented a random-effects model. Subgroup and sensitivity analyses were performed to investigate possible sources of heterogeneity and ensure the reliability of results[17,18]. Publication bias was assessed using funnel plots and statistical tests such as Egger[8].

3. Results

3.1. Characteristics of the included studies

The initial database search generated 823 articles, with 49 duplicates eliminated. After the evaluation of titles and abstracts, 683 articles were excluded. For the remaining 91 articles, a thorough full-text review was performed, resulting in the exclusion of 40 studies for various reasons. Ultimately, seven studies with a total of 6 711 participants met the selection criteria. The process of screening literature is depicted in Figure 1, while the records[8,19–24] extracted from the search are illustrated in Table 1.

3.2. Association and comparison details

The analysis concentrated on seven specific studies involving a total of 6711 participants and 15087 semen samples. The primary objective was to investigate the association between ambient SO_2 exposure and semen quality parameters. Subgroup analyses were conducted to explore potential sources of heterogeneity, including factors such as study design, semen analysis method, and body mass index (BMI).

To assess the methodological quality and potential bias inherent in the analyzed studies, the Newcastle-Ottawa scale was employed. The grading system outlined in Table 2 concentrates on three principal domains: participant selection, group comparisons, and the evaluation of results or exposure. The assigned scores for the quality assessment of each article ranged from 4 to 8 (Table 2).

This comprehensive approach deepened our comprehension of the association between SO_2 exposure and semen quality while shedding light on potential contributors to heterogeneity.

3.3. Relationship between semen quality outcomes and ambient particulate matters

3.3.1. Meta-analysis

The meta-analysis revealed a significant relationship between ambient SO_2 exposure and semen quality outcomes. The pooled analysis indicated statistically non-significant decreases in seminal fluid volume (PC=-0.009; 95% *CI*: -0.048 to -0.030; *P*=0.66), total sperm count (PC=-0.038; 95% *CI*: -0.079 to 0.003; *P*=0.07), and sperm motility (PC=-0.17; 95% *CI*: -0.363 to 0.022; *P*=0.83); However, these decreases did not reach statistical significance.

In addition, participants exposed to SO_2 showed a significant reduction in sperm concentration (PC=-0.020; 95% *CI*: -0.036 to -0.005; *P*=0.012) and progressive motility (PC=0.032; 95% *CI*: -0.063 to -0.001; *P*=0.044). The results of the meta-analysis are visually represented in Figure 2 using forest plots.

3.3.2. Subgroup analysis

Subgroup analyses were conducted to explore potential sources of heterogeneity and assess the impact of specific factors on the association between ambient SO_2 and progressive motility (Table 3). These analyses considered factors such as study design (cross-sectional or longitudinal), semen analysis method [computer-assisted sperm analysis (CASA) or World Health Organization (WHO)-guided semen analysis], and BMI categories (<25 and ≥25 kg/m^2).

Table 1. Characteristics of the studies included in the systematic review and meta-analysis.

Author	Year	Country	Study design	No. of semen samples	Exposure assessment	Exposure window	Semen analysis method	Age, years Mean±SD	BMI, kg/m[3] Mean±SD	Outcomes
Cheng *et al*[19]	2022	China	Cross-sectional study	1607	IDW model	Lag 0–90 days lag 0–1 year	WHO-guided semen analysis	30.9±4.2	25.7±2.8	Semen volume, sperm concentration, total sperm number, total motility, progressive motility
Liu *et al*[20]	2017	China	Longitudinal study	2184	IDW model	Lag 0–9, lag 10–14, lag 70–90, lag 0–90 days	WHO-guided semen analysis	29.8±8.9	27.3±3.9	Sperm concentration, total sperm number, total motility, progressive motility
Huang *et al*[21]	2020	China	Longitudinal study	3797	Ground-level monitoring station	Lag 0–9, lag 10–14, lag 70–90, lag 0–90 days lag 0–1 year	WHO-guided semen analysis	26.0±5.9	22.5±3.4	Sperm concentration, total sperm number, total motility, progressive motility
Qiu *et al*[22]	2020	China	Longitudinal study	4841	Chengdu metropolitan monitor stations	Lag 0–90 days	WHO-guided semen analysis	27.78±5.35	22.57±2.43	Semen volume, sperm concentration, total sperm number, progressive motility
Radwan *et al*[8]	2015	Poland	Cross-sectional study	285	Air quality information system	Lag 0–90 days	CASA	32.3±4.4	26.8±3.4	Sperm concentration, total sperm number, total motility
Yang *et al*[23]	2021	China	Longitudinal study	1991	China network environment monitoring center	Lag 0–9, lag 10–14, lag 70–90, lag 0–90 days	CASA	25.61±4.99	22.34±1.97	Sperm concentration, total sperm number, total motility, progressive motility
Zhou *et al*[24]	2020	China	Cross-sectional study	382	Ordinary-Kriging model	Lag 0–9, lag 10–14, lag 70–90, lag 0–90 days	WHO-guided semen analysis	29.71±4.08	26.3±3.2	Semen volume, sperm concentration, total sperm number, total motility

BMI: body mass index; CASA: computer-assisted semen analysis; IDW: inverse distance weighting; SD: standard deviation.

Table 2. Quality assessment of studies included in this meta-analysis based on the Newcastle-Ottawa scale.

Author	Year	Selection				Comparability	Exposure			Score
		An adequate definition of case	Representativeness of the case	Selection of controls	Definition of controls	Cases and controls matched and/or adjusted by factors	Assessment of exposure	The same method of ascertainment for cases and controls	The same response rate for both groups	
Cheng *et al*	2022	*	*	–	*	*	*	*	–	6
Liu *et al*	2017	*	*	*	*	**	*	-	*	8
Huang *et al*	2020	*	*		*	*	*	*	-	6
Qiu *et al*	2020	*	*	*	*	*	*	-	*	7
Radwan *et al*	2015	*	*	–	*	**	*	*	*	8
Yang *et al*	2021	*	*	-	*	*	*	*	*	7
Zhou *et al*	2020	*	*	*	*	*	*	*	–	7

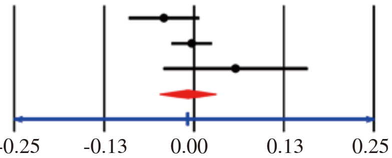
The quality assessment criteria for Newcastle-Ottawa scale include three major aspects: (a) Selection of subjects, for which a score between 0 to 4 points is allotted. (b) Subject comparability, which is allotted a score between 0 to 2 points. (c) Clinical outcome, for which a score between 0 to 3 points is given. In case of any discrepancies between the two investigators, a thorough discussion is held in the presence of a third investigator acting as an adjudicator to resolve the issue.

A

Study name	Log scale β	Standard error	Variance	Lower limit	Upper limit	Z-value	P-value
Cheng 2022	-0.042	0.025	0.001	-0.091	0.007	-1.673	0.094
Qiu 2020	-0.003	0.014	0.000	-0.031	0.025	-0.216	0.829
Zhou 2020	0.058	0.051	0.003	-0.043	0.158	1.129	0.259
Pooled	-0.009	0.020	0.000	-0.048	0.030	-0.438	0.661
Prediction interval	-0.009			-0.395	0.378		

Statistics for each study

Std diff in means and 95%*CI*



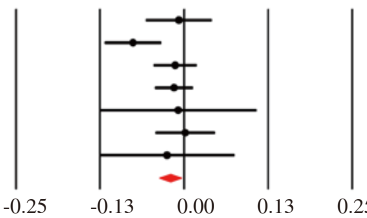
Random effects model, heterogeneity, overall I^2: 44.32

B

Study name	Log scale β	Standard error	Variance	Lower limit	Upper limit	Z-value	P-value
Cheng 2022	-0.008	0.025	0.001	-0.057	0.041	-0.307	0.759
Liu 2017	-0.076	0.021	0.000	-0.118	-0.034	-3.544	0.000
Huang 2020	-0.013	0.016	0.000	-0.045	0.019	-0.810	0.418
Qiu 2020	-0.015	0.014	0.000	-0.043	0.013	-1.038	0.299
Radwan 2015	-0.009	0.059	0.004	-0.125	0.107	-0.147	0.883
Yang 2021	0.002	0.022	0.001	-0.042	0.046	0.074	0.941
Zhou 2020	-0.025	0.051	0.003	-0.126	0.075	-0.496	0.620
Pooled	-0.020	0.008	0.000	-0.036	-0.005	-2.514	0.012

Statistics for each study

Std diff in means and 95%*CI*



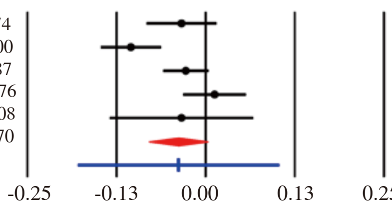
Fixed effects model, heterogeneity, overall I^2: 28.06

C

Study name	Log scale β	Standard error	Variance	Lower limit	Upper limit	Z-value	P-value
Cheng 2022	-0.034	0.025	0.001	-0.083	0.015	-1.359	0.174
Liu 2017	-0.105	0.021	0.000	-0.147	-0.063	-4.880	0.000
Huang 2020	-0.028	0.016	0.000	-0.060	0.004	-1.710	0.087
Yang 2021	0.013	0.022	0.001	-0.031	0.056	0.559	0.576
Zhou 2020	-0.034	0.051	0.003	-0.134	0.066	-0.661	0.508
Pooled	-0.038	0.021	0.000	-0.079	0.003	-1.810	0.070
Prediction interval	-0.038			-0.179	0.103		

Statistics for each study

Std diff in means and 95%*CI*



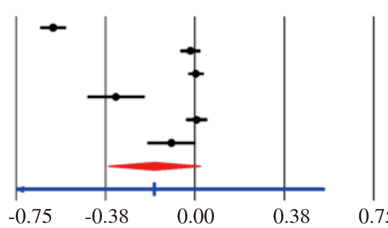
Random effects model, heterogeneity, overall I^2: 73.64

D

Study name	Log scale β	Standard error	Variance	Lower limit	Upper limit	Z-value	P-value
Cheng 2022	-0.595	0.027	0.001	-0.648	-0.542	-21.986	0.000
Liu 2017	-0.019	0.021	0.000	-0.060	0.023	-0.865	0.387
Huang 2020	0.004	0.016	0.000	-0.028	0.036	0.260	0.795
Radwan 2015	-0.331	0.061	0.004	-0.450	-0.212	-5.445	0.000
Yang 2021	0.007	0.022	0.001	-0.037	0.051	0.328	0.743
Zhou 2020	-0.098	0.051	0.003	-0.199	0.002	-1.916	0.055
Pooled	-0.170	0.098	0.010	-0.363	0.022	-1.734	0.083
Prediction interval	-0.170			-0.885	0.544		

Statistics for each study

Std diff in means and 95%*CI*



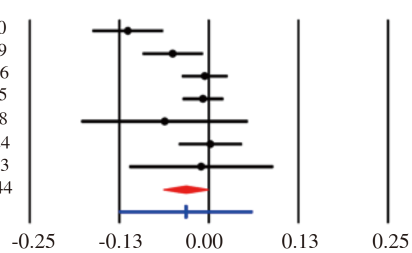
Random effects model, heterogeneity, overall I^2: 78.42

E

Study name	Log scale β	Standard error	Variance	Lower limit	Upper limit	Z-value	P-value
Cheng 2022	-0.113	0.025	0.001	-0.162	-0.064	-4.519	0.000
Liu 2017	-0.050	0.021	0.000	-0.092	-0.008	-2.354	0.019
Huang 2020	0.006	0.016	0.000	-0.037	0.026	-0.350	0.726
Qiu 2020	-0.008	0.014	0.000	-0.036	0.020	-0.576	0.565
Radwan 2015	-0.062	0.059	0.004	-0.178	0.054	-1.041	0.298
Yang 2021	0.002	0.022	0.001	-0.042	0.046	0.096	0.924
Zhou 2020	-0.011	0.051	0.003	-0.111	0.089	-0.211	0.833
Pooled	-0.032	0.016	0.000	-0.063	0.001	-2.013	0.044
Prediction interval	-0.032			-0.125	0.061		

Statistics for each study

Std diff in means and 95%*CI*



Random effects model, heterogeneity, overall I^2: 67.56

Figure 2. Forest plots show the relationship between SO_2 exposure and the following semen parameters: semen volume (A), sperm concentration (B), total sperm count (C), total motility (D), and progressive motility (E).

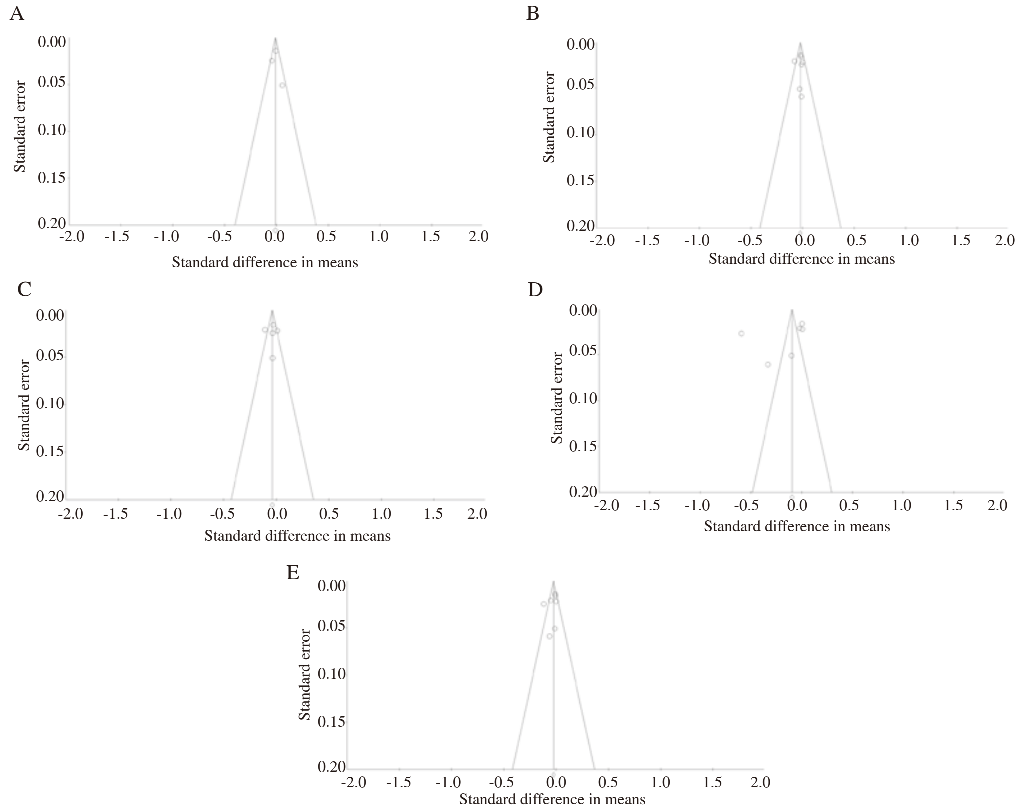


Figure 3. Funnel plot to assess the presences of publication bias about SO_2 exposure and semen parameters, including A) semen volume, B) sperm concentration, C) total sperm count, D) total motility, and E) progressive motility.

Table 3. Subgroup meta-analysis of the included studies.

Subgroup analysis	No. studies/ samples	Test of association		Heterogeneity	
		ES (95% *CI*)	*P* value	I^2	*P* value
Study design					
Cross-sectional	3/2274	-0.076 (-0.142, -0.009)	0.027	46.55	0.150
Longitudinal study	4/12813	-0.014 (-0.033, 0.006)	0.179	21.45	0.280
Semen analysis method					
CASA	2/2371	-0.006 (-0.048, 0.036)	0.773	1.48	0.310
WHO-guided semen analysis	5/12716	-0.038 (-0.078, 0.001)	0.059	77.13	<0.010
BMI, kg/m^2					
<25	3/10629	-0.005 (-0.024, 0.014)	0.578	0.00	0.926
≥25	4/4458	-0.068 (-0.114, -0.023)	0.003	46.85	46.85

ES: effect ssize, *CI*: confidence interval, CASA: computer-assisted semen analysis, BMI: body mass index.

The results demonstrated consistent associations between ambient SO_2 and semen quality outcomes across different subgroups, indicating the robustness of the observed relationship. The overall pooled effect in the subgroup analysis remained consistent across various potential sources of heterogeneity. The cross-sectional group exhibited lower semen quality in men (PC=-0.076; 95% *CI*: -0.142 to -0.009; *P*=0.027), indicating a significant correlation between the study design and semen quality parameters following exposure to SO_2. Furthermore, a significant relationship was found between BMI 25 kg/m^2 studies and lower semen quality parameters following exposure to SO_2 (PC = -0.068; 95% *CI*: -0.114 to -0.023; *P*>0.05).

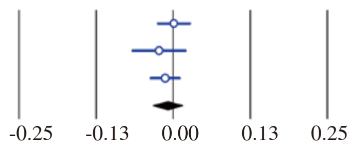
3.3.4. Sensitivity analysis and publication bias

Publication bias was assessed using Egger's test and visual inspection of the funnel plot. These tests revealed no significant evidence of publication bias [(semen volume coefficient: 0.674; standard error (SE): 2.450; 95% *CI*: -30.45 to 29.80, *P*=0.828), (sperm concentration coefficient: -0.137; SE: 1.246; 95% *CI*: -3.34 to 3.06, *P*=0.916), (total sperm count coefficient: -0.079; SE: 3.308; 95% *CI*: -10.60 to 10.40, *P*=0.982), (total motility coefficient: -9.146; SE: 1.941; 95% *CI*: -36.74 to 18.45, *P*=0.409), progressive motility coefficient: -1.542; SE: 1.776; 95% *CI*: -6.10 to 3.02, *P*=0.424)]. These data are supported by the symmetrical distribution of data points in the funnel plot (Figure 3). A sensitivity analysis was performed to assess the robustness of the meta-analysis results. Removing each study from the analysis did not significantly change the overall conclusions, indicating the stability of the findings (Figure 4).

A

Study name	Point	Standard error	Variance	Lower limit	Upper limit	*Z*-value	*P*-value
Cheng 2022	0.001	0.014	0.000	-0.026	0.028	0.097	0.923
Qiu 2020	-0.023	0.022	0.001	-0.067	0.021	-1.010	0.313
Zhou 2020	-0.013	0.012	0.000	-0.037	0.012	-1.022	0.307
Pooled	-0.009	0.012	0.000	-0.033	0.015	-0.727	0.467

Statistics with study removed

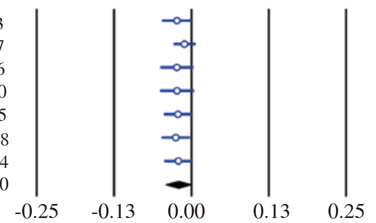


Sensitity analysis

B

Study name	Point	Standard error	Variance	Lower limit	Upper limit	*Z*-value	*P*-value
Cheng 2022	-0.023	0.012	0.000	-0.047	0.000	-1.938	0.053
Liu 2017	-0.011	0.009	0.000	-0.028	0.006	-1.262	0.207
Huang 2020	-0.024	0.013	0.000	-0.050	0.003	-1.772	0.076
Qiu 2020	-0.023	0.014	0.000	-0.050	0.004	-1.698	0.090
Radwan 2015	-0.022	0.011	0.000	-0.044	0.000	-1.923	0.055
Yang 2021	-0.025	0.012	0.000	-0.048	-0.003	-2.199	0.028
Zhou 2020	-0.021	0.011	0.000	-0.043	0.001	-1.852	0.064
Pooled	-0.021	0.010	0.000	-0.041	-0.001	-2.051	0.040

Statistics with study removed

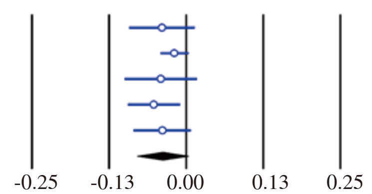


Sensitity analysis

C

Study name	Point	Standard error	Variance	Lower limit	Upper limit	*Z*-value	*P*-value
Cheng 2022	-0.039	0.027	0.001	-0.092	0.014	-1.441	0.150
Liu 2017	-0.019	0.011	0.000	-0.041	0.003	-1.676	0.094
Huang 2020	-0.041	0.030	0.001	-0.100	0.018	-1.371	0.170
Yang 2021	-0.052	0.021	0.000	-0.094	-0.010	-2.442	0.015
Zhou 2020	-0.039	0.024	0.001	-0.085	0.008	-1.633	0.102
Pooled	-0.038	0.021	0.000	-0.079	-0.003	-1.810	0.070

Statistics with study removed

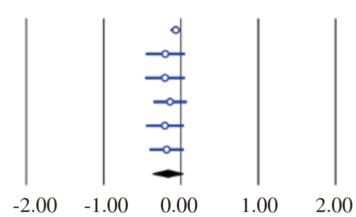


Sensitity analysis

D

Study name	Point	Standard error	Variance	Lower limit	Upper limit	*Z*-value	*P*-value
Cheng 2022	-0.064	0.035	0.001	-0.132	0.003	-1.862	0.063
Liu 2017	-0.202	0.127	0.016	-0.450	0.046	-1.594	0.111
Huang 2020	-0.207	0.129	0.017	-0.460	0.046	-1.600	0.110
Radwan 2015	-0.140	0.108	0.012	-0.351	0.072	-1.297	0.195
Yang 2021	-0.207	0.123	0.015	-0.449	0.035	-1.679	0.093
Zhou 2020	-0.185	0.111	0.012	-0.402	0.033	-1.664	0.096
Pooled	-0.170	0.098	0.010	-0.363	0.022	-1.734	0.083

Statistics with study removed

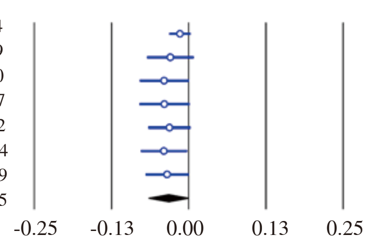


Sensitity analysis

E

Study name	Point	Standard error	Variance	Lower limit	Upper limit	*Z*-value	*P*-value
Cheng 2022	-0.014	0.009	0.000	-0.031	0.003	-1.628	0.104
Liu 2017	-0.030	0.019	0.000	-0.067	0.008	-1.557	0.119
Huang 2020	-0.040	0.020	0.000	-0.079	0.000	-1.964	0.050
Qiu 2020	0.039	0.021	0.000	0.080	0.001	1.906	0.057
Radwan 2015	-0.031	0.017	0.000	-0.065	0.003	-1.797	0.072
Yang 2021	-0.040	0.019	0.000	-0.077	-0.003	-2.116	0.034
Zhou 2020	-0.035	0.018	0.000	-0.069	0.000	-1.970	0.049
Pooled	-0.033	0.016	0.000	-0.065	-0.001	-2.003	0.045

Statistics with study removed



Sensitity analysis

Figure 4. Sensitivity analysis plot of SO_2 exposure and semen parameters, including A) semen volume, B) sperm concentration, C) total sperm count, D) total motility, and E) progressive motility.

4. Discussion

Our systematic review and meta-analysis focused on examining the association between SO_2 exposure and semen quality parameters and highlighted the potential impact of air pollution on male reproductive health. The findings of this study provide critical insights into the effects of SO_2 on semen quality and underscore the importance of understanding the impact of air pollution on human fertility. The results of the current meta-analysis indicate a clear link between exposure to environmental SO_2 and adverse effects on semen quality parameters, specifically total sperm count, total motility, and progressive motility. The findings demonstrate that higher levels of SO_2 in the environment are associated with a decrease in total sperm count, total motility, and progressive motility. Moreover, significant declines were observed in both sperm concentration and progressive sperm motility parameters. These results are consistent with previous studies investigating the relationship between air pollution and sperm quality and support the idea of the harmful effects of air pollution on male reproductive health[22,23].

Subgroup analyses were performed to investigate potential sources of heterogeneity and determine the impact of specific factors on the relationship between ambient SO_2 and progressive mobility. These analyses considered various factors, such as study design (cross-sectional or longitudinal), method of semen analysis (CASA or WHO-guided analysis), and BMI categories (less than 25 kg/m^2 and greater than or equal to 25 kg/m^2)[25,26]. The findings indicated that studies with higher BMI and longer follow-up periods in longitudinal studies exhibited larger effect size values. Furthermore, studies that adhered to WHO guidelines experienced more pronounced changes in sperm motility.

The association between environmental SO_2 pollution and decreased sperm quality raises essential questions about the biological mechanisms involved. One explanation in this case is the ability of SO_2 and other air pollutants to cause oxidative stress in sperm. Oxidative stress is caused by the excessive production of reactive oxygen species (ROS) and their overcoming the body's antioxidant defense system[27]. There are several evidences that increased oxidative stress significantly affects sperm motility, concentration, and morphology through mechanisms such as plasma membrane damage, DNA damage, and sperm apoptosis. Therefore, oxidative stress and its associated parameters are among the most critical predictors of sperm health[28,29]. The findings of an additional study indicate that SO_2 exposure induces an elevation in H_2O_2 levels[4]. This rise in H_2O_2 concentration subsequently reduces NADPH levels, constraining the antioxidant defense mechanism and promoting membrane peroxidation. Moreover, it results in an elevation of ROS, which ultimately impacts sperm quality[28,30]. A simulated study also discovered that exposure to SO_2 particles can trigger oxidative stress by activating endoplasmic reticulum stress, decreasing sperm quality[31]. Another factor that may affect sperm quality is inflammatory injury. Inflammatory injury affects the male reproductive system and can disrupt its function, leading to changes in sperm function[32]. Exposure to air pollution, particularly SO_2, can lead to inflammation through the release of proinflammatory cytokines and particles[33]. Inflammatory mediators have the potential to affect the function of the blood barrier in the testicles. They can interrupt hormone production, disrupt the microenvironment that is necessary for sperm growth, and lower the quality of sperm[34]. Exposure to air pollutants containing endocrine-disrupting chemicals (EDCs) may adversely affect sperm quality by disrupting the endocrine system. Endocrine-disrupting chemicals disrupt every aspect of hormone function responsible for maintaining homeostasis and regulating growth processes. It is widely understood that these compounds can have detrimental effects on production by impeding the hormone-dependent metabolic pathways responsible for the growth of gonads. This interference can occur through direct interaction with hormone receptors, disrupting their balance, or through epigenetic methods and regulation of cell cycles[35]. Several studies have demonstrated significant decreases in fertility biomarkers, particularly sperm count, and poor sperm performance in human populations exposed to these compounds[36–39].

The systematic review and meta-analysis performed possess several strengths that enhance the validity and reliability of the findings. Through amalgamating outcomes from numerous studies, an overall effect size estimation was achieved, elevating the statistical robustness of the analysis. Moreover, the focus centered explicitly on the impacts of airborne SO_2, facilitating a more profound comprehension of this specific air pollutant's effects on semen quality. In addition, our comprehensive assessment of several semen quality parameters, including sperm concentration, total sperm count, motility, and morphology, provides an overview of the effects of SO_2 on various aspects of semen quality.

Despite these strengths, our study has limitations that should be considered. First, the included studies were mostly observational, which limits our ability to establish a causal relationship between environmental SO_2 exposure and sperm quality. Further, prospective cohort or experimental studies must confirm the observed associations and clarify the underlying mechanisms. Second, the heterogeneity of the included studies, resulting from differences in study design, population characteristics, exposure assessment methods, and semen quality analysis, may have led to different results. Although we performed meta-regression and subgroup analyses to examine potential sources of heterogeneity, residual heterogeneity may still exist. Another limitation is that most of the studies included relied on city-level air pollution data or indirect exposure assessment methods, which may lead to exposure misclassification. Future research should aim to incorporate individual-level exposure data at higher spatial resolution to improve the accuracy of exposure assessment. In addition, most of the included studies were conducted in specific regions, which may limit the generalizability of our findings to other populations and geographic regions. Future studies must include more diverse populations from different regions to improve the external validity of the results.

In conclusion, this systematic review and meta-analysis provide compelling evidence for the negative correlation between ambient SO_2 exposure and semen quality. The findings highlight the importance of recognizing air pollution, particularly SO_2, as a potential risk factor for male reproductive health. In addition, they highlight the need for further research to validate these associations and investigate preventive measures to reduce the adverse effects of SO_2 pollution on semen quality.

Conflict of interest statement

The authors declare no conflicts of interest to disclose.

Acknowledgments

The authors would like to express their gratitude to the researchers whose articles were utilized in this study.

Funding

The study received no extramural funding.

Authors' contributions

Seyed Sobhan Bahreiny and Dr. Moslem Javidan designed the study, collected all the data, and drafted the manuscript. Mojtaba Aghaei and Dr. Hamid Ghorbani also contributed to the search strategy, article search, study selection, and manuscript preparation. Dr. Reza Mohammadpour Fard and Seyed Sobhan Bahreiny analyzed and interpreted the scientific data and results. Finally, all authors have read and approved the final manuscript.

References

[1] Kampa M, Castanas E. Human health effects of air pollution. *Environ Pollut* 2008; **151**(2): 362-367.

[2] Khaniabadi YO, Polosa R, Chuturkova RZ, Daryanoosh M, Goudarzi G, Borgini A, et al. Human health risk assessment due to ambient PM_{10} and SO_2 by an air quality modeling technique. *Process Saf Environ Prot* 2017; **111**(10): 346-354.

[3] Pandey JS, Kumar R, Devotta S. Health risks of NO_2, SPM and SO_2 in Delhi (India). *Atmos Environ* 2005; **39**(36): 6868-6874.

[4] Iwasawa S, Kikuchi Y, Nishiwaki Y, Nakano M, Michikawa T, Tsuboi T, et al. Effects of SO_2 on respiratory system of adult Miyakejima resident 2 years after returning to the island. *J Occup Health* 2009; **51**(1): 38-47.

[5] Singh GK, Rai S, Jadon N. Major ambient air pollutants and toxicity exposure on human health and their respiratory system: A review. *J Environ Manag Tour* 2021; **7**(55): 1774-1788.

[6] Mikkelsen AT, Madsen SA, Humaidan P. Psychological aspects of male fertility treatment. *J Adv Nurs* 2013; **69**(9): 1977-1986.

[7] Wdowiak A, Wdowiak E, Bień A, Bojar I, Iwanowicz-Palus G, Raczkiewicz D. Air pollution and semen parameters in men seeking fertility treatment for the first time. *Int J Occup Med Environ Health* 2019; **32**(3): 387-399.

[8] Radwan M, Jurewicz J, Polańska K, Sobala W, Radwan P, Bochenek M, et al. Exposure to ambient air pollution-does it affect semen quality and the level of reproductive hormones? *Ann Hum Biol* 2016; **43**(1): 50-56.

[9] Jurewicz J, Hanke W, Radwan M, Bonde JP. Environmental factors and semen quality. *Int J Occup Med Environ Health* 2009; **22**(4): 305-329.

[10] Sideri S, Papageorgiou SN, Eliades T. Registration in the international prospective register of systematic reviews (PROSPERO) of systematic review protocols was associated with increased review quality. *J Clin Epidemiol* 2018; **100**: 103-110.

[11] Bahreiny SS, Dabbagh MR, Ebrahimi R, Harooni E. Prevalence of autoimmune thyroiditis in women with polycystic ovary syndrome: A systematic review and meta-analysis. *Iran J Obstet Gynecol Infertil* 2023; **26**(1): 94-106.

[12] Moons KG, de Groot JA, Bouwmeester W, Vergouwe Y, Mallett S, Altman DG, et al. Critical appraisal and data extraction for systematic reviews of prediction modelling studies: The CHARMS checklist. *PLoS Med* 2014; **11**(10): e1001744.

[13] Luchini C, Stubbs B, Solmi M, Veronese N. Assessing the quality of studies in meta-analyses: Advantages and limitations of the Newcastle Ottawa Scale. *World J Meta–Anal* 2017; **5**(4): 80-84.

[14] Bahreiny SS, Harooni E, Dabbagh MR, Ebrahimi R. Circulating serum preptin levels in women with polycystic ovary syndrome: A systematic review and meta-analysis. *Int J Reprod Biomed* 2023; **21**(5): 367-378.

[15] Benoit K. *Linear regression models with logarithmic transformations*. London: London School of Economics; 2011, p. 23-36.

[16] Wells G, Tugwell P, Shea B, Guyatt G, Peterson J, Zytaruk N, et al. Meta-analyses of therapies for postmenopausal osteoporosis. V. Meta-analysis of the efficacy of hormone replacement therapy in treating and preventing osteoporosis in postmenopausal women. *Endocr Rev* 2002; **23**(4): 529-539.

[17] Andrade C. Mean difference, standardized mean difference (SMD), and their use in meta-analysis: As simple as it gets. *J Clin Psychiatry* 2020; **81**(5): 11349.

[18] Challis S, Nielssen O, Harris A, Large M. Systematic meta-analysis of the risk factors for deliberate self-harm before and after treatment for first-episode psychosis. *Acta Psychiatr Scand* 2013; **127**(6): 442-454.

[19] Cheng Y, Tang Q, Lu Y, Li M, Zhou Y, Wu P, et al. Semen quality and sperm DNA methylation in relation to long-term exposure to air pollution in fertile men: A cross-sectional study. *Environ Pollut* 2022; **300**: 118994.

[20] Liu Y, Zhou Y, Ma J, Bao W, Li J, Zhou T, et al. Inverse association between ambient sulfur dioxide exposure and semen quality in Wuhan,

China. *Environ Sci Technol* 2017; **51**(21): 12806-12814.

[21]Huang G, Zhang Q, Wu H, Wang Q, Chen Y, Guo P, et al. Sperm quality and ambient air pollution exposure: A retrospective, cohort study in a Southern province of China. *Environ Res* 2020; **188**: 109756.

[22]Qiu Y, Yang T, Seyler BC, Wang X, Wang Y, Jiang M, et al. Ambient air pollution and male fecundity: A retrospective analysis of longitudinal data from a Chinese human sperm bank (2013–2018). *Environ Res* 2020; **186**: 109528.

[23]Yang T, Deng L, Sun B, Zhang S, Xian Y, Xiao X, et al. Semen quality and windows of susceptibility: A case study during COVID-19 outbreak in China. *Environ Res* 2021; **197**: 111085.

[24]Zhou L, Li L, Hao G, Li B, Yang S, Wang N, et al. Sperm mtDNA copy number, telomere length, and seminal spermatogenic cells in relation to ambient air pollution: Results of a cross-sectional study in Jing-Jin-Ji region of China. *J Hazard Mater* 2021; **406**: 124308.

[25]Soler C, Valverde A, Bompart D, Fereidounfar S, Sancho M, Yániz J, et al. New methods of semen analysis by casa. *Sel´skokhozyaistvennaya Biol* 2017; **52**(2): 232-241.

[26]Bahreiny SS, Ahangarpour A, Hemmati AA, Kazemzadeh R, Bastani M-N, Dabbagh MR, et al. Circulating nesfatin-1 levels in women with polycystic ovary syndrome: A systematic review and meta-analysis. *Int J Reprod Biomed* 2023; **21**(10): 777-788.

[27]Tremellen K. Oxidative stress and male infertility-A clinical perspective. *Hum Reprod Update* 2008; **14**(3): 243-258.

[28]Agarwal A, Prabakaran SA. Mechanism, measurement, and prevention of oxidative stress in male reproductive physiology. *Indian J Exp Biol* 2005; **43**(11): 963-974.

[29]Kao SH, Chao HT, Chen HW, Hwang TIS, Liao TL, Wei YH. Increase of oxidative stress in human sperm with lower motility. *Fertil Steril* 2008; **89**(5): 1183-1190.

[30]Li X, Yi H, Wang H. Sulphur dioxide and arsenic affect male reproduction *via* interfering with spermatogenesis in mice. *Ecotoxicol Environ Saf* 2018; **165**(11): 164-173.

[31]Liu H, Ding S, Nie H, Shi Y, Lai W, Liu X, et al. PM(2.5) exposure at different concentrations and modes induces reproductive toxicity in male rats mediated by oxidative and endoplasmic reticulum stress. *Ecotoxicol Environ Saf* 2022; **244**: 114042.

[32]Bachir BG, Jarvi K. Infectious, inflammatory, and immunologic conditions resulting in male infertility. *Urol Clin North Am* 2014; **41**(1): 67-81.

[33]Meng Z, Liu Y, Wu D. Effect of sulfur dioxide inhalation on cytokine levels in lungs and serum of mice. *Inhal Toxicol* 2005; **17**(6): 303-307.

[34]Zheng P, Chen Z, Shi J, Xue Y, Bai Y, Kang Y, et al. Association between ambient air pollution and blood sex hormones levels in men. *Environ Res* 2022; **211**: 113117.

[35]Sifakis S, Androutsopoulos VP, Tsatsakis AM, Spandidos DA. Human exposure to endocrine disrupting chemicals: Effects on the male and female reproductive systems. *Environ Toxicol Pharmacol* 2017; **51**: 56-70.

[36]Jouannet P, Wang C, Eustache F, Kold-Jensen T, Auger J. Semen quality and male reproductive health: The controversy about human sperm concentration decline. *Apmis* 2001; **109**(5): 333-344.

[37]Perry MJ, Venners SA, Barr DB, Xu X. Environmental pyrethroid and organophosphorus insecticide exposures and sperm concentration. *Reprod Toxicol* 2007; **23**(1): 113-118.

[38]Slutsky M, Levin JL, Levy BS. Azoospermia and oligospermia among a large cohort of DBCP applicators in 12 countries. *Int J Occup Environ Health* 1999; **5**(2): 116-122.

[39]Safe S. Endocrine disruptors and falling sperm counts: Lessons learned or not! *Asian J Androl* 2013; **15**(2): 191-194.

Publisher's Note

The Publisher of the *Journal* remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Edited by Lin LY, Lei Y