Environmental Research 189 (2020) 109894

Contents lists available at ScienceDirect

Environmental Research

journal homepage: www.elsevier.com/locate/envres

Identifying critical exposure windows for ambient air pollution and semen quality in Chinese men

Shengzhi Sun [a], Jinzhu Zhao [b,1,**], Wangnan Cao [c], Wenqing Lu [d,e], Tongzhang Zheng [f], Qiang Zeng [d,e,f,1,*]

[a] Department of Environmental Health, Boston University School of Public Health, 715 Albany Street, Boston, MA, 02118, USA
[b] Department of Pediatrics, Tongji Hospital, Tongji Medical College, Huazhong University of Science & Technology, PR China
[c] Center for Evidence Synthesis in Health, Brown University School of Public Health, Providence, RI, 02912, USA
[d] Department of Occupational and Environmental Health, School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, PR China
[e] Key Laboratory of Environment and Health, Ministry of Education & Ministry of Environmental Protection, State Key Laboratory of Environmental Health (incubating), School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, PR China
[f] Department of Epidemiology, Brown University School of Public Health, Providence, RI, 02906, USA

ARTICLE INFO

Keywords:
Air pollution
Semen quality
Distributed lag model
Critical window

ABSTRACT

Emerging studies documented the association between ambient air pollution exposure and semen quality, but the critical exposure windows have not been comprehensively studied. To identify susceptible windows for associations of exposure to ambient respirable particulate matter (PM_{10}), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), and ozone (O_3) with sperm concentration, sperm count, total motility, and progressive motility, we recruited 1061 men attending an infertility clinic in Wuhan, China, between 2011 and 2013. We used a distributed lag multivariate linear regression to assess the exposure-lag-response relationship between semen quality and weekly air pollution exposure. The critical exposure windows were during the 6th to 12th sperm development weeks for PM_{10}, 10th to 11th weeks for O_3, and 0 to 5th weeks for SO_2. Over the entire 12 weeks of spermatogenesis period, an interquartile range increase (IQR) increase in PM_{10} was associated with declined sperm concentration [-45.64% (95% CI: −59.97%, −26.18%) percent decrease], declined sperm count [-49.42% (95% CI: −64.42%, −28.09%) percent decrease], reduced total motility [-12.42 (95% CI: −20.47, −4.37)], and reduced progressive motility [-8.81 (95% CI: −16.00, −1.61)], SO_2 per IQR increase was associated with reduced sperm concentration [-39.73% (95% CI: −55.96%, −17.51%) percent decrease] and total motility [-8.64 (95% CI: −16.90, −0.38)], but NO_2 and O_3 were not associated with any of the four sperm quality parameters. Our findings suggest that exposure to PM_{10} during spermatidogenesis period, exposure to SO_2 during spermatocytogenesis period, and exposure to O_3 during spermiogenesis period were associated with impaired semen quality, which implies air pollutants impair semen quality through varied pathways.

1. Introduction

Infertility is a global public health problem. In 2010, an estimated 48.5 million couples worldwide were infertile (Mascarenhas et al., 2012), and pure men factors accounted for 20%–30% of the problem (Agarwal et al., 2015; Sharlip et al., 2002). It was estimated that the average sperm count and sperm concentration had dropped by 60% and 52%, respectively, and the declining trend was still ongoing according to a recent meta-analysis (Levine et al., 2017).

Emerging studies examined the association of air pollution with semen quality (Table S1) (Carré et al., 2017; Najafi et al., 2015), and findings are inconsistent with some (Hammoud et al., 2010; Huang, 2019; Lao et al., 2018; Liu et al., 2017; Radwan et al., 2016; Rubes et al., 2007a; Selevan et al., 2000a; Sokol et al., 2005; Wang, 2019; Wu et al.,

* Corresponding author. Department of Occupational and Environmental Health, School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, PR China.
** Corresponding author.
E-mail addresses: zengqiang506@163.com, qiang_zeng@brown.edu (Q. Zeng).
[1] Qiang Zeng and Jinzhu Zhao as corresponding authors equally contribute to this work.

https://doi.org/10.1016/j.envres.2020.109894
Received 3 March 2020; Received in revised form 28 June 2020; Accepted 29 June 2020
Available online 11 July 2020

Table 1
Summary characteristics of the selected Chinese men in Wuhan, China (n = 1061).

Characteristics	N (%) or mean ± SD
Age, years	32.5 ± 5.2
BMI, kg/m^2	
<18.5	40 (3.8)
18.5–23.9	536 (50.5)
24.0–27.9	384 (36.2)
≥28.0	101 (9.5)
Ethnicity	
Han	1054 (99.3)
Other	7 (0.7)
Smoking status	
Never	429 (40.4)
Former	141 (13.3)
Current	489 (46.1)
Alcohol consumption	
Never	313 (29.5)
Sometimes	669 (63.1)
Frequent	77 (7.3)
Ever having fathered a child	
Yes	408 (38.5)
No	636 (59.9)
Educational attainment	
Middle school and lower	204 (19.2)
High school	278 (26.2)
College and higher	573 (54.0)
Household income, USD/month	
<290	136 (12.8)
290-580	446 (42.0)
>580	479 (45.1)
Abstinence period, days	
<3	89 (8.4)
3-5	698 (65.8)
≥6	274 (25.8)
Month	
March	119 (11.2)
April	259 (24.4)
May	477 (45.0)
June	187 (17.6)
July	19 (1.8)

Abbreviations: N = number of count; SD = standard deviation; BMI = body mass index.

2017; Zhang et al., 2019; Zhou et al., 2014, 2018), but not all studies find a negative association (Chen et al., 2019; Hansen et al., 2009; Nobles et al., 2018). Although the direct etiological mechanisms linking air pollution with the impaired semen quality remain unclear, it is hypothesized that hormonal disturbances, reactive oxygen species induction, cell DNA alteration, and epigenetic modification may play a role (Carré et al., 2017; Vecoli et al., 2016).

Identifying critical period of susceptibility for the association of air pollution with semen quality will improve our understanding of the underlying biological mechanisms and therefore target susceptible periods for clinical and public health interventions (Selevan et al., 2000b). Only a few studies (Hansen et al., 2009; Nobles et al., 2018; Sokol et al., 2005; Wang, 2019; Wu et al., 2017; Zhang et al., 2019) have explored windows of susceptibility, and some of these studies were only examined three time periods (e.g., 0–9, 10–14, 70–90 days before semen ejaculation), without showing the complete profile of the association along the sperm development cycle. In addition, these studies estimated the effects of air pollution during a given time period without taking into account of air pollution in the other exposure windows, which could result in biased estimates and identify incorrect critical windows (Wilson et al., 2017).

The distributed lag model is a data-driven method that could account for both the intensity and timing (lag) of past exposures and has been shown to obtain unbiased estimates to identify critical exposure windows (Gasparrini, 2014). To our knowledge, no study has applied this approach to identify the susceptible windows for the association between air pollution and semen quality.

Given the potential public health significance, we sought to examine the association of air pollution exposure during sperm development cycle with semen quality and to identify susceptible exposure windows using distributed lag multivariate linear models in Chinese men in Wuhan, China.

2. Material and methods

2.1. Participants

The study participants were from a subset population of our prior studies investigating the associations between environmental chemicals exposure and male reproductive health, which has been detailed elsewhere (Yang et al., 2016; Zeng et al., 2014). Briefly, between April 2011 and June 2013, we recruited men from sub-fertile couples who attended the Reproductive Center of Tongji Hospital for semen examination in Wuhan, China. After excluding azoospermia men and men with self-reported one of reproductive problems that might relate to impaired semen quality (e.g., vasectomy, epididymitis, vesiculitis, varicocele, injury of the testis, endocrine diseases), there were 3079 participants that were analysed in this study. Among them, 1061 men who had complete residential information in Wuhan were retained in the current study. Each participant signed written informed consent before participation. Ethics approval was obtained from the Ethics Committee of Tongji Medical College.

2.2. Information collection

Each study participant was asked to complete a questionnaire under trained investigators' guidance and provide a semen sample. The collected information included demographic characteristics (e.g., age and ethnic), lifestyle habits (e.g., smoking and drinking), medical history related to the reproductive system, and history of having ever fathered a child.

After reporting their number of abstinence days before semen ejaculation, participants were asked to masturbate into a sterile plastic specimen container in a semen collection room. The samplers were then liquefied in a heating chamber within 30 min. We used a serologic pipette to measure semen volume and tested sperm concentration and motility using a computer-aided semen analysis system according to the World Health Organization (WHO) guideline (Sharma et al., 2016; Zeng et al., 2013). We calculated sperm count by multiplying semen volume by sperm concentration. We also tested both progressive and non-progressive motility. Two professional technicians analysed semen samples were blinded to participants' information. For quality control, results from the two technicians were compared, and we found their results were not significant differences.

2.3. Air pollution assessment

Inverse distance weighting (IDW) was used to estimate daily concentrations of PM_{10}, NO_2, SO_2, and O_3 for each participant according to his residential address based on daily concentrations of air pollution measured from nine air quality monitoring stations between 2011 and 2013 in Wuhan, China (Brauer et al., 2008; Kim et al., 2014). IDW is commonly used to spatially interpolate air pollution concentrations at unmeasured sites using available measurements from surrounding fixed monitoring stations, with weights based on distances between the monitoring stations and the sites to be predicted (Gunnink and Burrough, 1996). The validation of using IDW in exposure assessment was assessed by the leave-one-out technique. For each air pollutant, the prediction accuracy was assessed by calculating the coefficient of determination, mean absolute error, and bias between predicted and measured concentrations (**Supplementary Material**). The coefficient of determination was 0.90 for PM_{10}, 0.77 for NO_2, 0.77 for SO_2, and 0.84

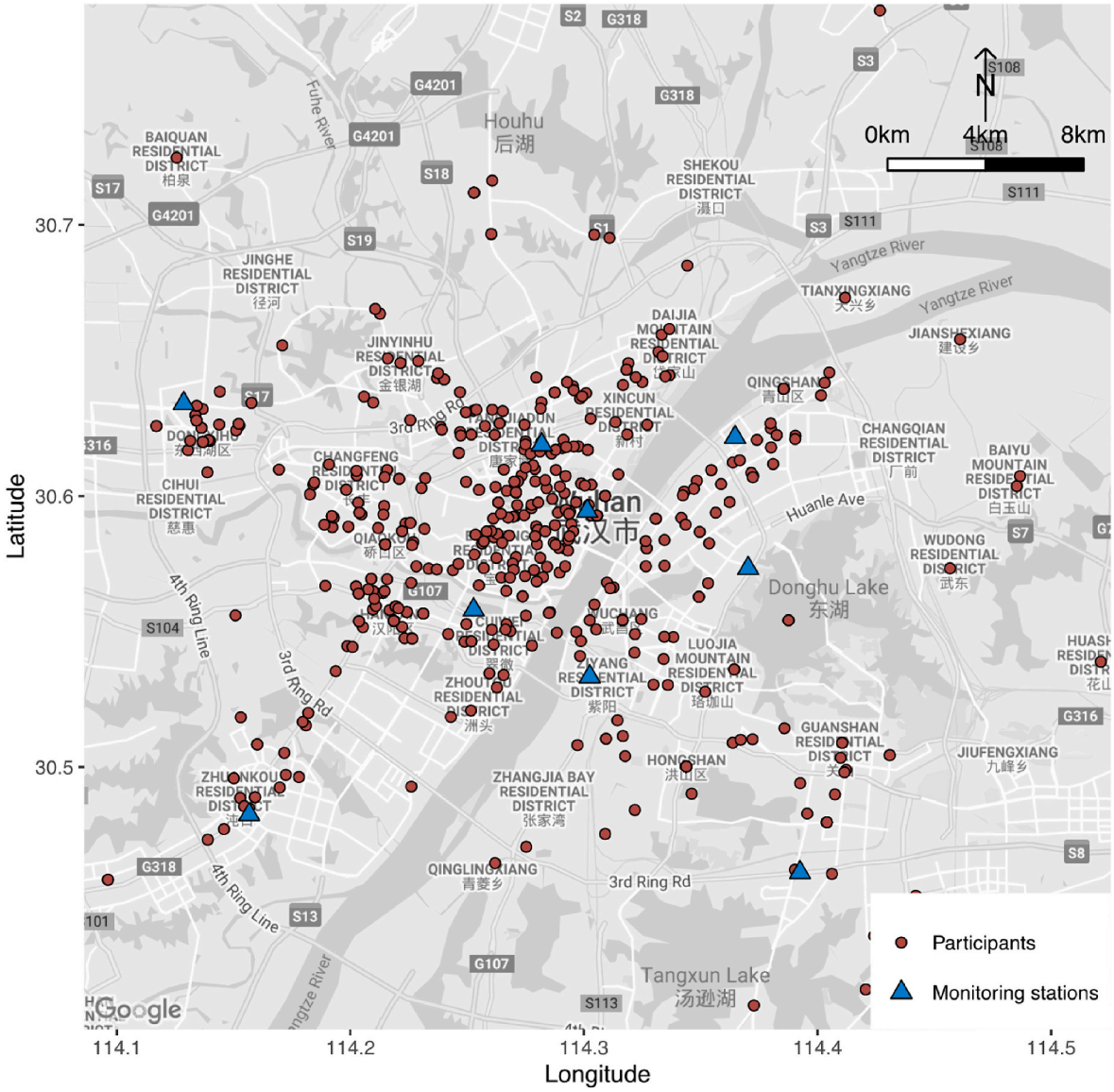

Fig. 1. Spatial distribution of air pollution monitoring stations (n = 9) and men (n = 1061) in Wuhan, China.

for O_3 (Table S2). We then calculated the weekly average air pollution exposure for each participant used the estimated daily air pollution data.

2.4. Statistical analysis

We applied a distributed lag multivariate linear regression to estimate the association of weekly air pollution exposure (PM_{10}, NO_2, SO_2, and O_3) during sperm development period with semen quality parameters (sperm concentration, sperm count, progressive motility, and total motility). We transformed sperm concentration and sperm count to approximate a normal distribution. We adjusted for age (<30 y, 30–34 y, 35–39 y, and >40 y), body mass index (BMI; <18.5 kg/m^2, 18.5–24.0 kg/m^2, 24.0–28.0 kg/m^2, and >28.0 kg/m^2), ethnicity (Han versus others), abstinence time (<3 d, 3–4 d, and >5 d), smoking status (never, former, or current), alcohol consumption (never, sometimes, or frequent), household income (<290 US$/month, 290–580 US$/month, or > 580 US$/month), educational attainment (middle school and lower, high school, or college and higher), ever having a child (yes versus no), and month (categorical) and year (continuous) of the sperm collection to control for the seasonality and long-term trend.

We used a distributed lag linear model to model both the exposure-response and time (lag)-response functions (Gasparrini, 2014). We used the minimize Akaike Information Criterion (AIC) to guide the selection of lag-response function (the relationships between air pollution and sperm parameters along weeks of sperm development period) and the corresponding degrees of freedom (Table S3) (Gasparrini, 2014).

Besides showing risk estimates of the association for each sperm development week, we also calculated the cumulative effects for 0 to 3rd, 4th to 10th, and 11th to 12th weeks of the spermatogenesis, which corresponds to periods of permatocytogenesis, spermatidogenesis, and spermiogenesis, as well as the entire 12 weeks of spermatogenesis (Amann, 2008). We expressed results as percent changes in sperm concentration and sperm count (log-transformed) or changes in total motility and progressive motility per interquartile range (IQR) increase in each pollutant.

To evaluate whether the association could still be observed among healthy participants, we excluded 330 participants with abnormal sperm concentration (<15 million/mL), sperm count (<39 million), total motility (<40% motile sperm) or progressive motility (<32% motile sperm) (Organization, 2010). We also additionally adjusted for co-pollutant one at a time when the Spearman correlation between the pollutant of interest and the co-pollutant was <0.6. We performed all

Table 2
Summary statistics for air pollutants and semen quality.

Variable	IQR	Mean ± SD	Percentile				
			Min	25th	50th	75th	Max
Air pollution (μg/m^3)							
PM_{10}	67.0	94.2 ± 45.5	14.5	59.0	83.8	126	273
NO_2	29.9	58.3 ± 23.1	18.4	40.9	54.6	70.9	168
SO_2	22.7	28.2 ± 16.4	3.2	15.4	25.9	38.1	83.8
O_3	81.3	104 ± 52.0	4.5	63.4	102	145	242
Semen quality parameters							
Concentration (millions/mL)	49.5	60.4 ± 44.7	4.0	28.5	50.2	78.0	334
Count (millions/sample)	150	170 ± 147	2	72	127	222	1197
Total motility (%)	28.7	53.1 ± 20.1	0.0	39.9	53.3	68.6	95.5
Progressive motility (%)	25.7	45.0 ± 17.9	0.0	33.0	45.1	58.7	86.9

Abbreviations: PM_{10} = particulate matter with aerodynamic diameter ≤ 10 μm; NO_2 = nitrogen dioxide; SO_2 = sulfur dioxide; O_3 = ozone; IQR = interquartile range; SD = standard deviation; Min = minimum; Max = maximum.

analyses in R software (Version 3.6.1) with package "dlnm" (version 2.3.9) for the distributed lag models.

3. Results

The basic characteristics of the participants were summarized in Table 1. Between 2011 and 2013, a total of 1061 men were included in our study, more than half of them were enrolled in April and May, and the majority (99.3%) were Han. The mean age at semen collection was 32.5 (SD: 5.2) years. About half of the participants were overweight or obese (45.7%) or current-smoker (46.1%). Before the semen examination, most men (74.2%) were abstinent for three or more days. Fig. 1 shows the spatial distribution of air pollution monitoring stations (n = 9) and the studied men (n = 1064).

The IQR of air pollutants on the day of semen examination were 67.0 μg/m^3 for PM_{10}, 29.9 μg/m^3 for NO_2, 22.7 μg/m^3 for SO_2, and 81.3 μg/m^3 for O_3 (Table 2). The mean (SD) of sperm quality parameters were 60.4 (44.7) millions/mL for sperm concentration, 170 (147) millions/sample for sperm count, 53.1% (20.1%) for total motility, and 45.0% (17.9%) for progressive motility.

The Spearman correlations among air pollutants or semen quality parameters were generally moderate to high ($r > 0.5$) (Fig. 2). For example, the correlation between PM_{10} and NO_2 ($r = 0.76$) and the correlation between sperm concentration and sperm count ($r = 0.76$). Whereas the correlations between air pollution and semen quality parameters were generally low to moderate ($r < 0.5$). For example, the correlation between SO_2 and sperm concentration ($r = 0.02$), sperm count ($r = 0.01$), total motility ($r = 0.03$), and progressive motility ($r = 0.03$).

We found the association of semen quality with air pollutants varied by weeks of the spermatogenesis (Fig. 3). The significant association between PM_{10} and impaired semen quality was during the 6th to 12th weeks. For example, an IQR (67.0 μg/m^3) increase in PM_{10} at the 9th week was associated with −6.34% (95% CI: −10.56%, −1.93%) percent reduction in sperm concentration, −5.43% (95% CI: −10.31%, −0.29%) percent reduction in sperm count, and a decrease of −1.78 (95% CI: −2.99, −0.57) in total motility and −1.27 (95% CI: −2.35, −0.19) in progressive motility. The critical exposure windows for SO_2 were during the 0 to 5th weeks. For example, the percent changes at the 1st weeks was −6.07% (95% CI: −10.46%, −1.46%) for sperm concentration, and −9.13% (95% CI: −14.00%, −3.99%) for sperm count per IQR (22.7 μg/m^3) increase in SO_2. We found the critical exposure windows for O_3 were at the 10th and 11th weeks for sperm concentration with percent

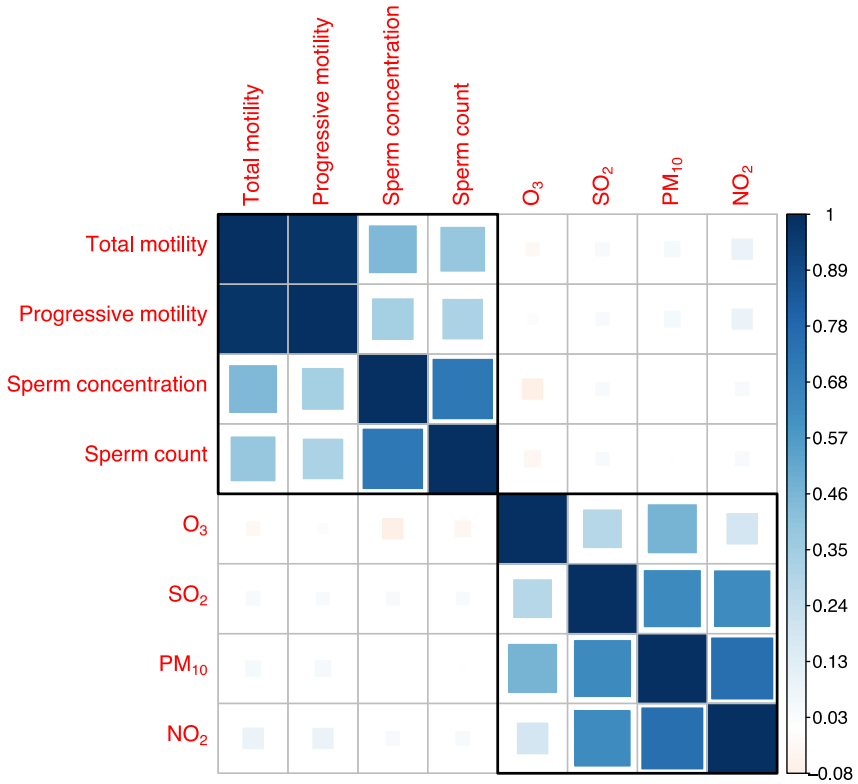

Fig. 2. Spearman correlation between air pollution and semen quality parameters. Size of the square is proportional to the correlation coefficients. Abbreviations: PM_{10} = particulate matter with aerodynamic diameter ≤10 μm; NO_2 = nitrogen dioxide; SO_2 = sulfur dioxide; O_3 = ozone.

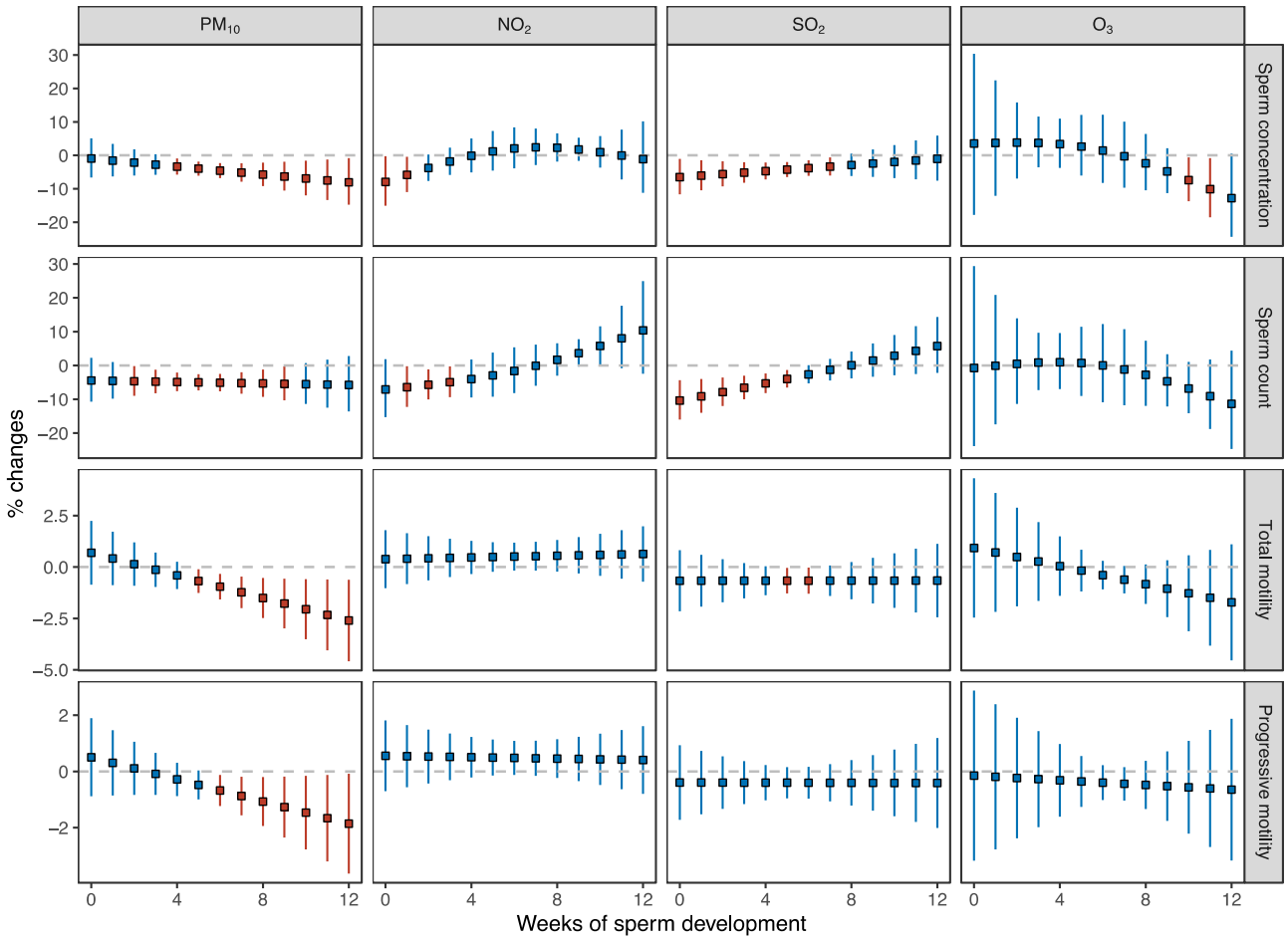

Fig. 3. The exposure-lag-response relationship between air pollution (per interquartile range increase) and semen quality parameters among 1061 men in Wuhan, China. Red colour represents that the risk estimates are statistically significant. Abbreviations: PM_{10} = particulate matter with aerodynamic diameter ≤10 μm; NO_2 = nitrogen dioxide; SO_2 = sulfur dioxide; O_3 = ozone. Models were adjusted for age (<30 y, 30–34 y, 35–39 y, and ≥40 y), body mass index (<18.5 kg/m^2, 18.5–23.9 kg/m^2, 24.0–27.9 kg/m^2, ≥28.0 kg/m^2), ethnic (Han versus others), smoking status (never, former, versus current smokers), alcohol consumption (never, sometimes, and frequent), ever having fathered a child (yes versus no), educational attainment (middle school and lower, high school, and college and higher), household income (>290 USD/month, 290–580 USD/month, and >580 USD/month), abstinence period (<3 d, 3–5 d, and ≥6 d), and month and year of sperm collection. . (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

changes were −7.41% (95% CI: −13.73%, −0.63%) and −10.11% (95% CI: −18.51%, −0.83%), respectively.

We further cumulated the risk estimates over the entire spermatogenesis period (0–12 weeks), 0–3 weeks (spermatocytogenesis period), 4–10 weeks (spermatidogenesis period), and 11–12 weeks (spermiogenesis period) (Table 3). Over the entire spermatogenesis period, exposure to higher level of PM_{10} were statistically significantly associated with impaired all four sperm quality parameters. An IQR (67.0 μg/m^3) increase in PM_{10} was associated with −45.64% (95% CI: −59.97%, −26.18%) percent reduction in sperm concentration, −49.42% (95% CI: −64.42%, −28.09%) percent reduction in sperm count, −12.42 (95% CI: −20.42, −4.37) reduction in total motility, and −8.81 (95% CI: −16.00, −1.61) reduction in progressive motility. We also found SO_2 was associated with declined sperm concentration [-39.73% (95% CI: −55.96%, −17.51%) percent reduction per IQR (22.7 μg/m^3) increase] and total motility [-8.64 (95% CI: −16.90, −0.38) reduction per IQR (22.7 μg/m^3) increase]. For the three key time periods, we found that PM_{10} were associated with reduced all four sperm quality parameters during period of spermatidogenesis, SO_2 during spermatocytogenesis period was negatively associated with sperm concentration and sperm count, and O_3 during spermiogenesis period was associated with a reduction in sperm concentration. However, we found little evidence of an association for NO_2 over the above four exposure periods.

Our findings were not materially different after excluding participants with abnormal sperm quality (Fig. S1) or additionally adjusted for co-pollutant (Table S4) in the sensitivity analyses.

4. Discussion

Among men attending an infertility clinic, we found PM_{10} exposure during the entire spermatogenesis period was associated with reduced sperm concentration, sperm count, total motility, and progressive motility, SO_2 was associated with declined sperm concentration and total motility, but NO_2 and O_3 was not associated with any of the four sperm quality parameters. The critical exposure windows were during the 6th to 12th weeks of spermatogenesis for PM_{10}, 0 to 5th weeks for SO_2, and 11th to 12th weeks for O_3.

Previous epidemiologic studies on the association of air pollution with semen quality have been mixed (Table S1). Although the association between air pollution and semen quality parameters was not statistically significant, a recent meta-analysis reported a suggestive negative association (Deng et al., 2016). The suggestive evidence of a negative association was also supported by another recent systematic review that included 17 relevant epidemiologic studies (Lafuente et al., 2016).

Most prior studies examined the effects of air pollution on sperm

Table 3
Percent changes or changes in semen quality parameters associated with an interquartile range increase in air pollution by exposure weeks among 1061 Chinese men in Wuhan, China.

Air pollutants	IQR (μg/m^3)	Weeks of sperm development	Sperm concentration (% changes in millions/mL)	Sperm count (% changes in millions/sample)	Total motility (%)	Progressive motility (%)
PM_{10}	67.0	0–3	−7.31 (−22.49, 10.84)	−17.23 (−32.61, 1.67)	1.12 (−3.58, 5.82)	0.83 (−3.37, 5.03)
		4–10	**−31.04 (-43.78, -15.41)**	**−31.27 (-45.66, -13.08)**	**−8.61 (-13.98, -3.24)**	**−6.12 (-10.92, -1.32)**
		11–12	**−14.96 (-26.14, -2.08)**	−11.08 (−24.39, 4.57)	**−4.93 (-8.64, -1.22)**	**−3.52 (-6.83, -0.21)**
		0–12	**−45.64 (-59.97, -26.18)**	**−49.42 (-64.42, -28.09)**	**−12.42 (-20.47, -4.37)**	**−8.81 (-16.00, -1.61)**
NO_2	29.9	0–3	**−18.17 (-32.30, -1.09)**	**−22.08 (-37.31, -3.15)**	1.66 (−2.96, 6.28)	2.14 (−1.98, 6.27)
		4–10	10.89 (−15.64, 45.76)	2.02 (−25.45, 39.63)	3.70 (−1.19, 8.59)	3.28 (−1.09, 7.64)
		11–12	−1.16 (−17.60, 18.55)	19.25 (−3.20, 46.92)	1.24 (−1.28, 3.77)	0.83 (−1.43, 3.08)
		0–12	−10.32 (−36.02, 25.72)	−5.20 (−35.65, 39.68)	6.60 (−2.23, 15.44)	6.24 (−1.64, 14.13)
SO_2	22.7	0–3	**−21.41 (-34.02, -6.39)**	**−29.91 (-42.69, -14.3)**	−2.67 (−7.28, 1.94)	−1.58 (−5.70, 2.53)
		4–10	**−21.30 (-35.39, -4.14)**	−8.72 (−27.25, 14.53)	−4.65 (−9.84, 0.55)	−2.83 (−7.47, 1.81)
		11–12	−2.56 (−14.17, 10.63)	10.30 (−4.69, 27.64)	−1.32 (−4.66, 2.02)	−0.82 (−3.81, 2.16)
		0–12	**−39.73 (-55.96, -17.51)**	−29.44 (−50.82, 1.23)	**−8.64 (-16.90, -0.38)**	−5.23 (−12.61, 2.15)
O_3	81.3	0–3	15.64 (−33.40, 100.82)	0.49 (−46.73, 89.54)	2.39 (−8.19, 12.97)	−0.85 (−10.29, 8.60)
		4–10	−7.71 (−42.96, 49.31)	−13.25 (−50.11, 50.84)	−4.3 (−8.97, 0.37)	−3.08 (−7.25, 1.08)
		11–12	**−21.62 (-38.22, -0.55)**	−19.41 (−38.71, 5.95)	−3.21 (−8.36, 1.94)	−1.25 (−5.85, 3.34)
		0–12	−16.34 (−41.03, 18.67)	−29.75 (−53.01, 5.01)	−5.12 (−14.14, 3.89)	−5.18 (−13.23, 2.86)

Abbreviations: PM_{10} = particulate matter with aerodynamic diameter ≤ 10 μm; NO_2 = nitrogen dioxide; SO_2 = sulfur dioxide; O_3 = ozone.
[a] 0–3 weeks correspond to spermatocytogenesis period; 4–10 weeks correspond to spermatidogenesis period; and 11–12 weeks correspond to spermiogenesis period. Models were adjusted for age (<30 y, 30–34 y, 35–39 y, and ≥40 y), body mass index (<18.5 kg/m^2, 18.5–23.9 kg/m^2, 24.0–27.9 kg/m^2, ≥28.0 kg/m^2), ethnicity (Han versus others), smoking status (never, former, versus current smokers), alcohol consumption (never, sometimes, and frequent), ever having fathered a child (yes versus no), educational attainment (middle school and lower, high school, and college and higher), household income (>290 USD/month, 290–580 USD/month, and >580 USD/month), abstinence period (<3 d, 3–5 d, and ≥6 d), and month and year of sperm collection.
The significance of bold in the table 3 is defined as p-value <0.05.

quality were over the entire sperm development period. Our findings of a negative association of semen quality with PM_{10} and SO_2 during the entire sperm production period were consistent with most of the prior studies (Hammoud et al., 2010; Huang, 2019; Lao et al., 2018; Liu et al., 2017; Nobles et al., 2018; Radwan et al., 2016; Rubes et al., 2007a; Wu et al., 2017; Zhou et al., 2014, 2018). For example, a US study conducted in Salt Lake County among 48 men evaluated for infertility, they found that $PM_{2.5}$ was associated with reduced sperm motility two to three months after exposure (Hammoud et al., 2010). Among 1759 men from sub-fertile couples undergoing assisted reproductive technology in Wuhan, China, SO_2 exposure over the entire sperm development period was associated with monotonically decreased sperm concentration, sperm count, and total motility (Liu et al., 2017).

Although the biological mechanisms to explain the link between air pollution exposure and the impaired semen quality are largely unclear, four potential mechanisms have been proposed: hormonal disturbances, reactive oxygen species induction, cell DNA alteration, and epigenetic modification. Acting of endocrine disruptors through suppression of Hypothalamus-Pituitary-Gonads axis (HPG), animal studies suggested that exposure to $PM_{2.5}$ significantly decreased follicle-stimulating hormone (FSH), circulating testosterone, and sperm count in the epididymis (Liu et al., 2018; Qiu et al., 2017). Most air pollutants are also associated with increased oxidative stress in the testicular microenvironment by excess reactive oxygen species (ROS) or decreased superoxide dismutase (SOD), one of the most important enzymes in protecting cells from ROS (Cao et al., 2017; Guo et al., 2012; Wei et al., 2018). Excess amount of ROS could damage the blood-testis barrier (BTB), alter sperm functions, and initiate chain reactions leading to apoptosis, resulting in poor semen quality (Agarwal and Allamaneni, 2011; Walczak–Jedrzejowska et al., 2013; Wei et al., 2018). Some air pollutants could also alter cell DNA by inducing excess ROS or by the formation of DNA adducts (Rubes et al., 2005). Finally, air pollutants have also been suggested to changes in DNA methylation, and therefore decrease spermatogenesis (Vecoli et al., 2016).

Identification of susceptible windows to environmental exposure is crucial for targeting public health interventions (Selevan et al., 2000b). We found that the declined semen quality was associated with exposure to PM_{10} at the period of spermatidogenesis (4–10 weeks), exposure to SO_2 at the period of spermatocytogenesis (0–3 weeks), and exposure to O_3 at the period of spermiogenesis (11–12 weeks). These varied critical exposure windows by air pollutants for semen quality could be explained by the interaction of multiple mechanisms induced by air pollutants. For example, three mechanisms may play a role in impairing semen quality for particulate matter (PM). It is suggested that PM could act as an endocrine disruptor affecting sperm motility through disrupting protein synthesis (Hammoud et al., 2010); it could also react with sperm DNA to form adducts resulting in disrupting late spermatogenesis (Rubes et al., 2007b). Additionally, PM could induce ROS, and therefore affect semen quality (Wei et al., 2018).

Our findings of the identified susceptible exposure windows are in line with a few epidemiologic studies that explored the exposure windows of susceptibility. For example, Rubes et al. (2005) and Hammound et al. (2010) suggested that PM could affect semen quality in the late stage of spermatogenesis through hormonal disturbances and cell DNA alteration (Hammoud et al., 2010; Rubes et al., 2007b). Wang, 2019 recruited 1852 men from an infertility clinic in central China and examined the association of sperm quality with SO_2 across 0–90, 0–9, 10–14, and 70–90 days prior to semen ejaculation, and they found that the adverse effect of SO_2 was more obvious in the early phase of spermatogenesis (Wang, 2019). However, our findings stand in contrast to 1

p.m. study that found that ambient exposure to particulate matter mainly affected the early stage of sperm development (Wu et al., 2017). Our study simultaneously controlled for air pollution exposures in other exposure windows using the distributed lag models, which could minimize bias in identifying critical windows (Wilson et al., 2017).

Our study has two main limitations. First, we did not measure personal air pollution exposure but used outdoor ambient air pollution concentrations estimated at the residential addresses as a proxy for individual exposures, which could introduce some degrees of exposure misclassification. However, we expect our results tend to toward of null association between air pollution and semen quality (Di et al., 2017; Sun, 2019). Second, our study population was men who attended an infertility clinic for semen examination. The proportion of men with poor semen quality is higher than the general population. Thus, the findings of our study generalized to the general population need to be cautious. On the other hand, our study is one of the largest sample sizes to systemically study the exposure-lag-response relationship between air pollution and semen quality.

5. Conclusions

In summary, among Chinese men attending an infertility clinic, we found evidence that air pollution was adversely associated with semen quality. Specifically, exposure to PM_{10} during spermatidogenesis period, exposure to SO_2 during spermatocytogenesis period, and exposure to O_3 during spermiogenesis period were associated with impaired semen quality. The findings of this study should shed light on targeting clinical and public health interventions.

Funding sources

This study was supported by the National and Key R&D Program of China (No. 2018YFC1004201) and the National Natural Science Foundation of China (No. 81872585).

Ethics approval was obtained from the Ethics Committee of Tongji Medical College.

Declaration of competing interest

None.

CRediT authorship contribution statement

Shengzhi Sun: Conceptualization, Writing - original draft, Formal analysis, Data curation, Investigation. **Jinzhu Zhao:** Conceptualization, Writing - review & editing, Resources, Data curation, Investigation. **Wangnan Cao:** Writing - review & editing. **Wenqing Lu:** Writing - review & editing. **Tongzhang Zheng:** Writing - review & editing. **Qiang Zeng:** Conceptualization, Methodology, Resources, Writing - review & editing, Funding acquisition.

Acknowledgements

We thank the doctors and nurses in the department for data and sample collection. This study was supported by the National and Key R&D Program of China (No. 2018YFC1004201) and the National Natural Science Foundation of China (No. 81872585).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2020.109894.

References

Agarwal, A., Allamaneni, S., 2011. Free radicals and male reproduction. J. Indian Med. Assoc. 109, 184–187.
Agarwal, A., et al., 2015. A unique view on male infertility around the globe. Reprod. Biol. Endocrinol. 13, 37.
Amann, R.P., 2008. The cycle of the seminiferous epithelium in humans: a need to revisit? J. Androl. 29, 469–487.
Brauer, M., et al., 2008. A cohort study of traffic-related air pollution impacts on birth outcomes. Environ. Health Perspect. 116, 680–686.
Cao, X.-n., et al., 2017. Urban fine particulate matter exposure causes male reproductive injury through destroying blood-testis barrier (BTB) integrity. Toxicol. Lett. 266, 1–12.
Carré, J., et al., 2017. Does air pollution play a role in infertility?: a systematic review. Environ. Health 16, 82.
Chen, Y., et al., 2019. The impact of the fine ambient particle on infertile male's sperm quality. Urol. Sci. 30, 177.
Deng, Z., et al., 2016. Association between air pollution and sperm quality: a systematic review and meta-analysis. Environ. Pollut. 208, 663–669.
Di, Q., et al., 2017. Association of short-term exposure to air pollution with mortality in older adults. Jama 318, 2446–2456.
Gasparrini, A., 2014. Modeling exposure–lag–response associations with distributed lag non-linear models. Stat. Med. 33, 881–899.
Gunnink, J., Burrough, P., 1996. Interactive Spatial Analysis of Soil Attribute Patterns Using Exploratory Data Analysis (EDA) and GIS. Spatial Analytical Perspectives on GIS. Taylor Francis, New York, pp. 87–99.
Guo, L., et al., 2012. Particulate matter (PM10) exposure induces endothelial dysfunction and inflammation in rat brain. J. Hazard Mater. 213, 28–37.
Hammoud, A., et al., 2010. Decreased sperm motility is associated with air pollution in Salt Lake City. Fertil. Steril. 93, 1875–1879.
Hansen, C., et al., 2009. The effect of ambient air pollution on sperm quality. Environ. Health Perspect. 118, 203–209.
Huang, X., et al., 2019. Association of exposure to ambient fine particulate matter constituents with semen quality among men attending a fertility center in China. Environ. Sci. Technol. 53 (10), 5957–5965.
Kim, E., et al., 2014. Prenatal exposure to PM10 and NO2 and children's neurodevelopment from birth to 24 months of age: mothers and Children's Environmental Health (MOCEH) study. Sci. Total Environ. 481, 439–445.
Lafuente, R., et al., 2016. Outdoor air pollution and sperm quality. Fertil. Steril. 106, 880–896.
Lao, X.Q., et al., 2018. Exposure to ambient fine particulate matter and semen quality in Taiwan. Occup. Environ. Med. 75, 148–154.
Levine, H., et al., 2017. Temporal trends in sperm count: a systematic review and meta-regression analysis. Hum. Reprod. 23, 646–659.
Liu, J., et al., 2018. Fine particle matter disrupts the blood–testis barrier by activating TGF-β3/p38 MAPK pathway and decreasing testosterone secretion in rat. Environ. Toxicol. 33, 711–719.
Liu, Y., et al., 2017. Inverse association between ambient sulfur dioxide exposure and semen quality in Wuhan, China. Environ. Sci. Technol. 51, 12806–12814.
Mascarenhas, M.N., et al., 2012. National, regional, and global trends in infertility prevalence since 1990: a systematic analysis of 277 health surveys. PLoS Med. 9, e1001356.
Najafi, T.F., et al., 2015. Air pollution and quality of sperm: a meta-analysis. Iran. Red Crescent Med. J. 17.
Nobles, C.J., et al., 2018. Ambient air pollution and semen quality. Environ. Res. 163, 228–236.
Organization, W.H., 2010. WHO Laboratory Manual for the Examination and Processing of Human Semen.
Qiu, L., et al., 2017. Exposure to concentrated ambient pm2.5 compromises spermatogenesis in a mouse model: role of suppression of hypothalamus-pituitary-gonads axis. Toxicol. Sci. 162, 318–326.
Radwan, M., et al., 2016. Exposure to ambient air pollution-does it affect semen quality and the level of reproductive hormones? Ann. Hum. Biol. 43, 50–56.
Rubes, J., et al., 2007a. Impact of Air Pollution on Reproductive Health in Northern Bohemia. Reproductive Health and the Environment. Springer, pp. 207–224.
Rubes, J., et al., 2005. Episodic air pollution is associated with increased DNA fragmentation in human sperm without other changes in semen quality. Hum. Reprod. 20, 2776–2783.
Rubes, J., et al., 2007b. GSTM1 genotype influences the susceptibility of men to sperm DNA damage associated with exposure to air pollution. Mutat. Res. 625, 20–28.
Selevan, S.G., et al., 2000a. Semen quality and reproductive health of young Czech men exposed to seasonal air pollution. Environ. Health Perspect. 108, 887–894.
Selevan, S.G., et al., 2000b. Identifying critical windows of exposure for children's health. Environ. Health Perspect. 108, 451–455.
Sharlip, I.D., et al., 2002. Best practice policies for male infertility. Fertil. Steril. 77, 873–882.
Sharma, R., et al., 2016. Cigarette smoking and semen quality: a new meta-analysis examining the effect of the 2010 World Health Organization laboratory methods for the examination of human semen. Eur. Urol. 70, 635–645.
Sokol, R.Z., et al., 2005. Exposure to environmental ozone alters semen quality. Environ. Health Perspect. 114, 360–365.
Sun, S., et al., 2019. Benefits of physical activity not affected by air pollution: a prospective cohort study. Int. J. Epidemiol. 49 (1), 142–152.
Vecoli, C., et al., 2016. Environmental pollutants: genetic damage and epigenetic changes in male germ cells. Environ. Sci. Pollut. Res. 23, 23339–23348.

Walczak–Jedrzejowska, R., et al., 2013. The role of oxidative stress and antioxidants in male fertility. Cent. Eur. J. Urol. 66, 60.
Wang, X., et al., 2019. Gaseous pollutant exposure affects semen quality in central China: a cross-sectional study. Andrology 8 (1), 117–124.
Wei, Y., et al., 2018. Urban fine particulate matter (PM2.5) exposure destroys blood–testis barrier (BTB) integrity through excessive ROS-mediated autophagy. Toxicol. Mech. Methods 28, 302–319.
Wilson, A., et al., 2017. Potential for Bias when estimating critical windows for air pollution in Children's health. Am. J. Epidemiol. 186, 1281–1289.
Wu, L., et al., 2017. Association between ambient particulate matter exposure and semen quality in Wuhan, China. Environ. Int. 98, 219–228.
Yang, P., et al., 2016. Urinary polycyclic aromatic hydrocarbon metabolites and human semen quality in China. Environ. Sci. Technol. 51, 958–967.
Zeng, Q., et al., 2013. Baseline blood trihalomethanes, semen parameters and serum total testosterone: a cross-sectional study in China. Environ. Int. 54, 134–140.
Zeng, Q., et al., 2014. Drinking-water disinfection by-products and semen quality: a cross-sectional study in China. Environ. Health Perspect. 122, 741–746.
Zhang, H.-T., et al., 2019. Ambient ozone pollution is associated with decreased semen quality: longitudinal analysis of 8945 semen samples from 2015 to 2018 and during pollution-control period in Beijing, China. Asian J. Androl. 21, 501–507.
Zhou, N., et al., 2014. Air pollution and decreased semen quality: a comparative study of Chongqing urban and rural areas. Environ. Pollut. 187, 145–152.
Zhou, N., et al., 2018. Exposures to atmospheric PM10 and PM10–2.5 affect male semen quality: results of MARHCS study. Environ. Sci. Technol. 52, 1571–1581.