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Research article

Effects of temperature anomaly on sperm quality: A multi-center study of 33,234 men

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A R T I C L E I N F O

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A B S T R A C T

Backgrounds: Global fertility rates continue to decline and sperm quality is a prime factor affecting male fertility. Both extreme cold and heat have been demonstrated to be associated with decreased sperm quality, but no epidemiological studies have considered human adaptation to long-term temperature. Our aim was to conduct a multi-center retrospective cohort study to investigate exposure-response relationship between temperature anomaly (TA) that deviate from long-term climate patterns and sperm quality.

Methods: A total of 78,952 semen samples measured in 33,234 donors from 6 provincial human sperm banks in China were collected. This study considered heat and cold acclimatization to prolonged exposure in humans and explored the exposure-response relationship between TAs and sperm quality parameters (sperm concentrations, sperm count, progressive motility, progressive sperm count, total motility and total motile sperm count) during the hot and cold seasons, respectively. Linear mixed models and generalized linear models were built separately for specific centers to pool in a meta-analysis to obtain the pooled effect of TA on sperm quality, considering repeated measurements data structure and spatial heterogeneity.

Results: We identified an inverted U-shaped exposure-response relationship between TA and sperm quality during the hot season. Significant negative effect of anomalous cold on sperm quality during the hot season was found after additional adjustment for Body mass index, marital status and childbearing history. The heat-related TA in hot season was significantly negatively associated with sperm concentration, progressive sperm count and total motile sperm count (all *P*-

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values<0.05). After adjusting the relative humidity, the cold-related TA in cold season was negatively associated with the sperm total motility (*P*-values<0.05).
Conclusions: Our results suggest both heat-related and cold-related TAs are associated with decreased sperm quality. The findings highlight the importance of reducing exposure to anomalous temperatures to protect male fertility.

1. Introduction

A growing number of studies indicate that a decline in the quality of human sperm is occurring. Studies in different countries around the world have reported a downward trend in male sperm quality in recent decades [1]. For example, Hagai Levine et al. showed a significant decrease in male sperm count in North America, Europe, Australia and New Zealand from 1973 to 2011 [2]. In addition, a recent meta-analysis demonstrated a decline in sperm count in men from South/Central America-Asia-Africa during the time period of 1973–2018 [3]. In a recent study, sperm count and progressive motility were also found to have declined in young Chinese men from 2001 to 2015 [4]. The decline of semen quality is a key factor affecting male fertility and even infertility. A previous study found that men alone may cause up to 30% of fertility problems, with the main cause being lower sperm count and quality of even up to 90% [5].

However, the causes of declining sperm quality are not yet conclusive. Several studies have shown the negative effects of meteorological factors on semen quality in men [6–8]. In the context of global climate change, extremely high or extremely low temperatures can lead to decreased sperm quality [9,10]. Indeed, the process of sperm development is affected by temperature, and failure of thermoregulation can be detrimental to sperm quality [11]. In particular, our latest study also demonstrated an association between temperature variability and decreased sperm quality in men [12]. However, current studies on the relationship between ambient temperature and sperm quality do not adequately consider the ability of humans to adapt to long-term changes in temperature. In addition, previous studies were mainly conducted by single centers and the results were difficult to generalize to other geographic regions with different climatic conditions. What is the impact of ambient temperature on male reproductive health in the context of global climate change and considering human adaption to long-term temperature changes? This question is still not well answered.

In fact, the health impacts of global climate change are a major public health threat in the world today [13,14]. According to the latest report of the Intergovernmental Panel on Climate Change (IPCC), global temperatures in 2011–2020 are 1.1 °C higher than in 1850–1900, and approximately 3.5 billion people live in environments highly vulnerable to climate change [15]. Most current studies of the health effects of climate change use average temperature as a measure [7,16,17], and few consider the effects of temperature change or even drastic change [18,19]. Some epidemiological studies have also explored the health effects caused by heat and cold weather at non-optimal temperatures [20–22], but with different non-optimal temperatures for different geographic regions. In order to reduce the impact of such bias, a metric that can take into account the heterogeneity caused by baseline temperature, temperature anomaly (TA), has been proposed [23]. In recent environmental epidemiology studies, this index has been successfully applied to investigate the expose-response relationship between anomalous weather and mortality as well as medical visits of patients [23–25]. However, the extent and mechanism of the effect of TA on male sperm quality still remains unclear. Previous studies have shown that both higher and lower temperatures are negatively associated with sperm quality [7], and prolonged heat or cold exposure causes humans heat or cold acclimatization [26,27]. This further suggests that it is necessary to investigate the associations between TA and

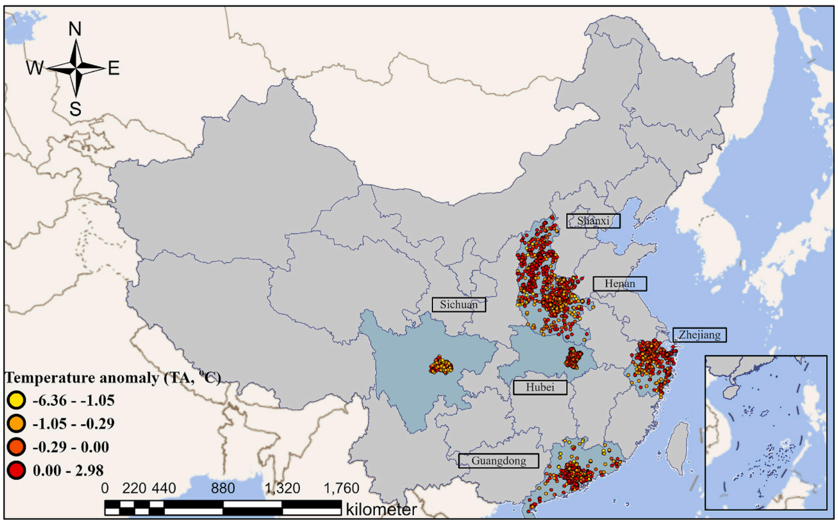

Fig. 1. Spatial distribution of residential addresses of all study subjects. The color indicates their lagged 0–90 days average temperature anomaly exposure level. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

semen quality separately in hot and cold seasons. In addition, sudden temperature changes may lead to adverse health events. Therefore, we also explored the association of anomalous hot or cold temperature exposure with sperm quality decline. To the best of our knowledge, this study represents the first attempt to explore the effect of TA on male sperm quality.

This multi-center population-based cohort study aimed to investigate the relationships between TA and sperm quality based on 78,952 semen samples measured in 33,234 male semen donors from 6 provincial human sperm banks covering several climatic zones in China. Moreover, we explored the exposure-response relationships between TA and sperm quality in hot and cold seasons, respectively. In particular, we focused on the effects of heat-related and cold-related TAs on sperm quality parameters.

2. Methods

2.1. Study subjects

This study initially collected 97,451 semen samples taken from 49,374 male volunteers who donated sperm between January 1, 2014 and December 31, 2020 from six Provincial Human Sperm Banks in China. The study areas covered Henan and Hubei provinces in central of China, Sichuan province in southwest of China, Shanxi province in north of China, Guangdong province in south of China, and Zhejiang province in east of China, respectively (Fig. 1). The six provinces included in the analysis were located in different climatic zones of China (Fig. S1). Each of the six Human Sperm Banks is located in the corresponding provincial capital, and semen donors are permanent local residents. In fact, different subjects donated semen different times, such as volunteers from Guangdong and Zhejiang provinces who donated semen samples several times. Accordingly, the interval between two donations is generally required to be at least 3–5 days. People in different provinces have different lifestyles and dietary habits, so to minimize the bias due to these unobservable confounders, we grouped individual provinces as a center. A two-stage analysis based on linear mixed models was performed to estimate the center-specific coefficients, and then pooled coefficients were derived within a meta-analysis framework. Our study screened and assessed volunteers according to the fifth edition of the World Health Organization Laboratory Manual for the Testing and Processing of Human Semen [28]. The inclusion criteria were: healthy men within the age range of 19–45 years; sperm donors with abstinence days in the range of 2–7 days. The exclusion criteria were also used: men with infectious diseases or other diseases; donors with missing residential address, ethnics and semen parameters; donors whose residential address was not within the study region; and unreasonable or illogical samples of ejaculation date and semen parameters. Eventually, a total of 78,952 semen samples from 33,234 sperm donors were included in this multi-center cohort study.

2.2. Semen analysis

The study outcome was sperm quality parameter including sperm concentration, sperm count, progressive motility, progressive sperm count, total motility and total motile sperm count [12,29]. For each volunteer, we generally recommend that should abstain for 2–7 days prior to sperm donation. Sperm donors used a designated sterile container in the semen collection room to collect the sample by masturbation. The semen samples collected to be liquefied in 37 °C water, and then tested and analyzed in less than 1 h. Under the guidance of the World Health Organization Laboratory Manual for the Detection and Processing of Human Semen [28], sperm concentration ($\times 10^6$/ml), semen volume (ml), sperm progressive motility (%) and total motility (%) were tested. Subjects in Sichuan and Shanxi provinces had missing data on sperm total motility. The sperm count ($\times 10^6$) was obtained by a multiplication of sperm concentration with semen volume and multiplying the progressive motility and total motility, respectively, to obtain progressive sperm count ($\times 10^6$) and total motile sperm count ($\times 10^6$). The six human sperm bank laboratories participate in the external quality control program of semen analysis organized by the Human Sperm Bank Technical Training Base of National Health Commission every year. The external quality control program includes semen quality parameters such as sperm concentration and sperm motility, and all laboratory operations comply with preset standards. Moreover, each sperm bank had implemented strict internal quality control procedures for semen analysis, and all technicians involved in the process were required to receive regular training in laboratory quality control.

2.3. Exposure assessment

The primary exposure factor in this study was temperature anomaly (TA), measuring the difference between the temperature exposure of subjects and the long-term temperature of their resident cities during the study period. We calculated TA using the following model [30]:

$$\mathrm{TM} \sim \mathrm{TA} + \mathrm{f}\,(\mathrm{d}),$$

where TM denotes the average temperature during the exposure period, f (d) is a smoothing term for the long-term average temperature of the exposure period, and d refers to the day of year (1–366). In this study, f (d) represents the average exposure temperatures for each day in each residential address over the entire 7 years of analysis [25]. Considering the entire period of sperm development, the exposure window of 0–90 days before ejaculation was used [31]. Therefore, TA is a measure of temperature anomaly for 0–90 days before sperm donation for each subject. Compared to the same address on the same month and day from 2014 to 2020, TA > 0 is defined as heat-related temperature anomaly (or anomalous heat) and TA < 0 is defined as cold-related temperature anomaly (or anomalous cold) [23]. An example of the derivation of temperature anomaly (TA) is provided in Supplementary Fig. S2. In order to capture the temperature exposure level of the subjects, a high-resolution prediction dataset was used to match to their residential address. The dataset of ERA5-Land reanalysis is an hourly gridded temperature data with a spatial resolution of $0.1^\circ \times 0.1^\circ$ [32]. Many studies have confirmed the validity and reliability of the ERA5-Land reanalysis dataset [33,34].

In addition, the association between $PM_{2.5}$ (Particles with diameter less than or equal to 2.5 μm in the atmosphere) and sperm quality has been demonstrated in previous study [35]. This study used the interquartile range (IQR) of $PM_{2.5}$ as a covariate to consider potential confounding factors. Due to the skewed distribution of $PM_{2.5}$, we used the median concentration to represent the exposure level of subjects during the 0–90 days prior to sperm donation [12]. The $PM_{2.5}$ concentration data used were derived from a high-precision and high-quality dataset at 1 km resolution, and the validity of the data was confirmed [36,37].

2.4. Statistical analysis

We conducted descriptive analysis on the sperm quality parameters and environmental exposure levels of the subjects. Specially, the spatial autocorrelation coefficient (Moran's *I*) is used to measure the spatial distribution characteristics of the study subjects. In addition, we also compared the distribution of exposure among subjects in six regions. The association between TAs and sperm quality parameters was estimated using a classical two-stage analysis.

In the first stage, we constructed a linear mixed model [38,39] with subject-specific random intercepts for the study samples from Guangdong and Zhejiang provinces, respectively, and a generalized linear model [40] for each of the other four regions (Henan, Hubei, Sichuan, and Shanxi provinces) with non-repeated measurement data. All models adjusted for potential confounders, including age (<30, 30–39, or ≥ 40 years), abstinence period (2–3 days, 4–5 days, or 6–7 days), ethnicity (Han, or others), year, season, and lagged 0–90 days median $PM_{2.5}$ concentration [12,35]. The exposure-response relations for average temperature and sperm quality parameters and TA and the parameters were compared. According to the histogram (Fig. S3), we found that sperm count did not obey the normal distribution. Thus before modeling we did BoxCox transformations on semen quality parameters to make them satisfy normal distribution [41]. And considering the comparability of the analysis, we also standardized so that the standard deviation (SD) and variance were both 1. The study hypothesized that both anomalous heat and cold exposure may be associated with a decrease in sperm quality and that sudden temperature changes may be more dangerous than gradual events of the same temperature change [12], modeling the TA as a natural cubic spline function with 3 degrees of freedom to capture the nonlinear association [9].

In the second stage, the center-specific coefficients and variances derived in the first stage were pooled in a meta-analysis [42]. The study used a random-effects model to obtain the pooled estimate of the nonlinear relationship between TA and each sperm quality parameter. Because prolonged heat and cold exposure can orient human adaptation to temperature differently [26,27], we analyzed semen samples collected during the hot and cold seasons separately. In this study, 1 Ma y to 31 October was defined as the hot season, and 1 November to 30 April the following year was defined as the cold season [43].

We performed several sensitivity analyses to verify the robustness of the study findings. First, the temperature anomaly (TA_{min}) was recalculated by using the daily minimum temperature instead of the daily average temperature, and we obtained the pooled estimate of the nonlinear association between TA_{min} and sperm quality parameters. Similarly, the temperature anomaly (TA_{max}) was calculated by the daily maximum temperature to perform the same analysis. Moreover, additional adjustment for covariates was made to account for the possible influence of other confounding factors, including the subject's BMI (<18.5, 18.5–23.9, 24.0–27.9, or ≥ 28.0 kg/m^2), marital status (unmarried, married, or divorced), and childbearing history (yes, or no). We excluded the samples with missing covariates and analyzed the remaining subgroup (n = 55,738). Third, we considered the spermatogenesis window of 55 days and explored the effect of TA exposure with a time lag of 0–55 days on sperm quality. Fourth, we only included the samples donated for the first time by the subjects who donated the samples repeatedly (n = 33,234) in the analysis to investigate the impact of repeated measurements on the results. Fifth, according to the occupation of donors (traffic police, open-air staff, students, and office staff, etc.), we divided the subjects into outdoor workers (n = 42,913) and indoor workers (n = 11,521) for subgroup analysis [44]. Finally, we additionally adjusted for the factor of relative humidity as a covariate in the model to evaluate the robustness of the results.

In addition, we performed separate subgroup analyses of heat-related and cold-related TAs exposure for each sperm quality parameter. The regression coefficients (β) and 95% confidence intervals (CIs) of the linear mixed models could be based on the results of SD changes to estimate the effect of each 1 °C change in temperature anomaly. For temperature exposure higher than the long-term temperature norm (TA > 0), we estimated changes in each semen quality parameter associated with per 1 °C increase of TA. For temperature exposure lower than the long-term temperature norm (TA < 0), estimated changes were assessed for per 1 °C decrease of TA. Since our previous study identified the associations between exposures to SO_2 and O_3 pollutants and sperm quality decline [45], we also performed sensitivity analysis by adjusting for SO_2 and O_3 in the models, respectively. Furthermore, we evaluated the associations between sperm quality and ambient TA exposure during three critical windows of sperm development including 0–9 days prior to ejaculation (epididymis storage), 10–14 days prior to ejaculation (development of sperm motility) and 70–90 days prior to ejaculation (spermatogenesis), respectively. We aimed to identify susceptible windows of TA exposure.

The study was completed using R software version 4.1 for all statistical analyses and corresponding visualization of results. The statistical tests involved in the study were all two-sided and statistically significant at a *P*-value <0.05. Geographic information visualization was done through ArcGIS version 10.2.

3. Results

3.1. Baseline characteristics of the subjects

A total of 78,952 semen samples were entered into this study, of which 41,983 (53%) samples were collected during the hot season (Table 1). Semen samples donated during the hot season had higher sperm concentration and count, but lower total sperm motility than samples collected during the cold season (all *P*-values <0.05). Guangdong and Zhejiang provinces provided 34,219 (43.3%) and 27,037 (34.2%) case samples, respectively. The average sperm concentration (121.51, SD: 65.58) and sperm count (410.64, SD: 277.24) were highest in subjects from Shanxi province. The average sperm concentration (41.90, SD: 22.93) and progressive motility (21.69, SD: 8.00) were the lowest in subjects from Hubei province. As shown in Table S1, subjects in Guangdong and Hubei provinces had relatively high mean temperature exposure levels during the 0–90 days prior to sperm donation (Median: 23.96, IQR: [19.39, 27.10]; Median: 20.35, IQR: [11.57, 25.12]), and subjects in Henan province had the lowest mean temperature exposure levels (Median: 12.77, IQR: [6.00, 20.85]). The indicator of TA is presented to make the different regions comparable (Fig. S4). The $PM_{2.5}$ exposure levels of subjects vary from region to region. Subjects in Henan province had the highest average $PM_{2.5}$ concentration exposure (Median: 74.17, IQR: [59.40, 95.79]), and subjects in Guangdong province had the lowest average exposure level (Median: 31.53, IQR: [25.22, 35.64]). Fig. S5 shows trends in semen quality and exposure to anomalous temperatures in 0–90 days prior to ejaculation during the study period. On the whole, the semen quality of men increased slightly and has a downward trend in the later period. The overall time trends in TA were first down and then up. In addition, we also performed spatial autocorrelation analysis to identify the spatial distribution patterns of sperm donors. We found that the spatial correlation of sperm donors included was small, and the distribution of the study subjects was relatively random (Moran's $I = 0.085$).

3.1.1. Exposure-response relationship analyses

Fig. S6 shows the center-specific exposure response relationship between ambient mean temperature and sperm quality. The adverse effects of high temperature on male sperm quality (Figs. S6a and S6b) were found in both Guangdong and Zhejiang provinces. The results from Henan, Hubei and Sichuan provinces show that low temperature had adverse effects on male sperm motility (Figs S6c, S6d and S6e). We found that the "optimal" temperatures of different centers are obviously different. Fig. S7 shows the center-specific exposure-response relationship between TA and sperm quality. In the regions with high baseline temperatures in Guangdong and Hubei provinces, TAs deviation from long-term temperature trends within a small range had a positive effect on sperm quality (Figs. S7a and S7d). We found an inverted U-shaped exposure response relationship between TAs and sperm quality in Zhejiang and Henan provinces (Figs. S7b and S7c). TA < 0 had a significant negative effect on sperm quality in subjects from Zhejiang Province, as well as on sperm concentration and total motility in subjects from Henan Province. TA > 0 showed a significant negative effect on the sperm counts of subjects from Zhejiang Province and the sperm quality of subjects from Henan Province. No significant association was found with the results from Sichuan and Shanxi provinces. A pooled exposure-response relationship plot is provided in Fig. S8. Although the confidence intervals were wide, an inverted U-shaped association of TA and sperm quality is still presented.

The pooled exposure-response relationship between temperature anomaly (TA) and semen quality separately in the hot and cold seasons is shown in Fig. 2. We found an inverted U-shaped curve between TA and sperm quality in the hot season (Fig. 2A-F). Anomalous heat during the hot season had a significant negative effect on sperm concentration and count (Fig. 2A and B). In addition,

Table 1
Descriptive statistics of semen parameters in the study sample from 2014 to 2020.

Characteristics	N (%)	Sperm concentration (10^6/ml) Mean ± SD	Sperm count (10^6) Mean ± SD	Progressive motility (%) Mean ± SD	Progressive sperm count (10^6) Mean ± SD	Total motility (%) Mean ± SD	Total motile sperm count (10^6) Mean ± SD
Total samples	789,52 (100)	72.52 ± 38.18	253.58 ± 158.74	50.69 ± 14.22	134.25 ± 95.11	55.39 ± 13.22	142.54 ± 95.98
Hot season	41,983 (53.2)	73.05 ± 38.52	255.45 ± 159.34	50.65 ± 14.19	134.98 ± 95.27	55.31 ± 13.21	143.39 ± 96.58
Cold season	36,969 (46.8)	71.92 ± 37.78	251.45 ± 158.02	50.73 ± 14.26	133.42 ± 94.93	55.47 ± 13.23	141.58 ± 95.28
Region							
Guangdong	34,219 (43.3)	83.42 ± 38.74	297.44 ± 159.68	56.02 ± 12.85	169.10 ± 100.25	59.34 ± 12.69	178.63 ± 104.16
Zhejiang	27,037 (34.2)	73.59 ± 33.54	269.70 ± 138.01	48.08 ± 10.16	131.13 ± 71.58	50.95 ± 10.25	139.17 ± 76.08
Henan	12,953 (16.4)	43.68 ± 21.36	117.66 ± 83.58	47.05 ± 16.30	60.94 ± 51.89	54.51 ± 16.28	69.63 ± 57.76
Hubei	2655 (3.4)	41.90 ± 22.93	121.39 ± 94.80	21.69 ± 8.00	25.93 ± 21.79	53.92 ± 14.60	67.44 ± 56.12
Sichuan	1150 (1.5)	78.78 ± 44.90	277.52 ± 170.09	57.29 ± 13.13	163.52 ± 112.15		
Shanxi	938 (1.2)	121.51 ± 65.58	410.64 ± 277.24	55.46 ± 9.46	236.11 ± 172.71		

SD: standardized deviation.

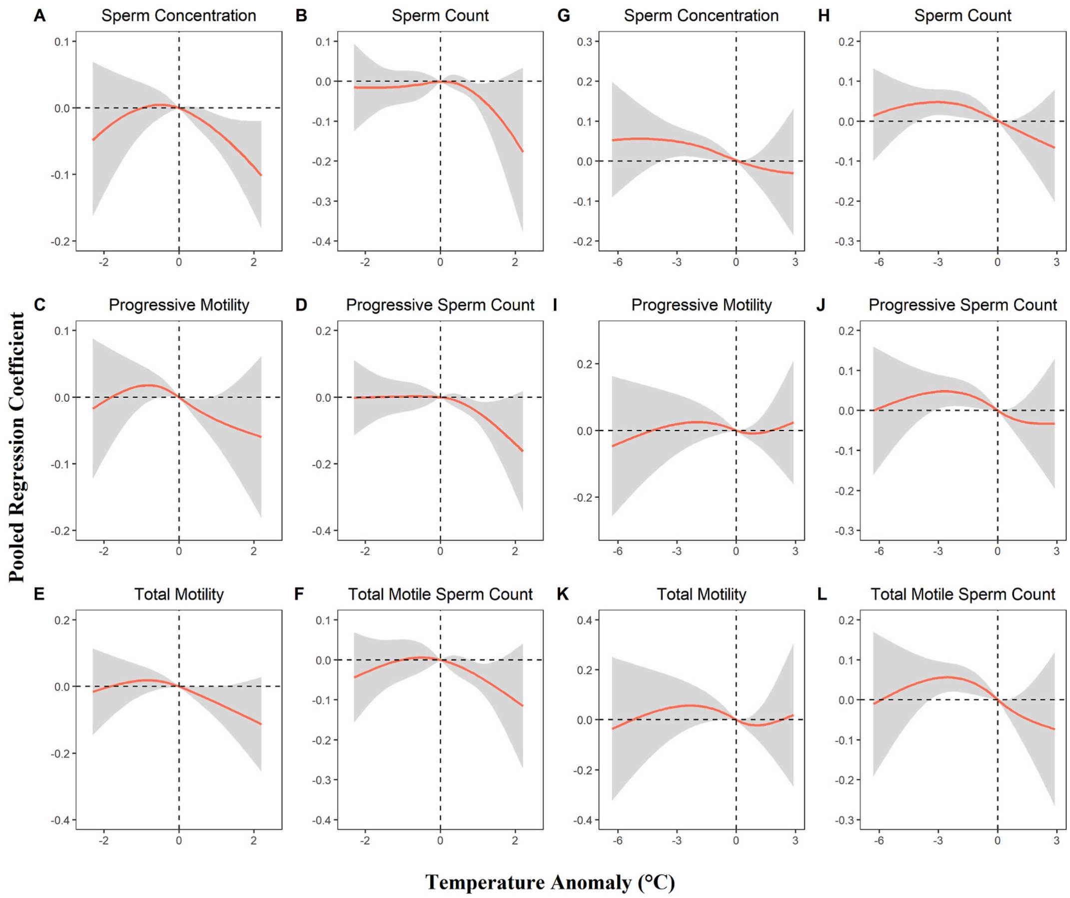

Fig. 2. Pooled exposure-response relationships between lagged 0–90 days temperature anomaly (TA) and sperm quality by hot and cold seasons during 2014–2020. The regression coefficients (red curves) and corresponding 95% confidence intervals (gray shading) were estimated for TA in the hot (A–F) and cold (G–L) seasons. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

motile sperm count also had a negative association with anomalous heat (Fig. 2D and F). There is a small upward trend in sperm count when TA deviates downward from the long-term temperature trend during the cold season (Fig. 2G, H, 2J and 2L), but the overall association remained an inverted U-shape. No significant association between sperm motility and temperature in cold season has been found (Fig. 2I and K). We observed the decline in sperm concentration (β: 0.035, 95% CI: [−0.061, −0.010]), sperm count (β: 0.036, 95% CI: [−0.067, −0.005]), progressive sperm count (β: 0.045, 95% CI: [−0.078, −0.012]), total motility (β: 0.049, 95% CI: [−0.097, −0.000]) and total motile sperm count (β: 0.040, 95% CI: [−0.072, −0.008]) in subjects with a 1 °C increase in temperature exposure level from the long-term temperature trend during the hot season (Table 2).

3.2. Sensitivity analyses

As shown in Fig. S9, the inverted U-shaped exposure response relationship between TA_{min} calculated by daily minimum temperature and sperm quality in the sensitivity analyses remained. Fig. S10 shows the results for TA_{max} calculated by daily maximum temperature. Although no statistically significant association was observed during the cold season, anomalous heat during the hot season clearly adversely affected sperm concentration and progressive motility and progressive sperm count (Figs S10A, S10C and S10D). In addition, there is a significant trend of decrease in total motile sperm count when exposed to extreme anomalously cold weather ($TA < -2$ °C) during the hot season (Fig. S10F). Fig. 3 shows the inverted U-shaped pattern of TAs and sperm quality parameters during the hot season was more significant after additional adjustment for BMI, marital status and childbearing history. The significance of the association between anomalous heat and sperm quality may become less due to the reduced sample size, but we observed a significant negative effect of anomalous cold also on sperm concentration, sperm count, progressive sperm count and total motile sperm count (Fig. 3A–F). When the temperature trend in the cold season deviates downwards, there is a small upward trend in sperm count (Fig. 3G, H, 3J, and 3L). No significant results were found in the larger range of temperature anomalies and changes in sperm motility (Fig. 3I–K).

Fig. S11 shows the exposure-response relationship between TA with a lag of 0–55 days and sperm quality. The anomalous high

Table 2
Nonlinear estimates between temperature anomaly and sperm quality by hot and cold seasons. All estimates are pooled results from the center-specific results (Reference: TA = 0).

	Exposure	Sperm concentration (10^6/ml) β (95% CIs)	Sperm count (10^6) β (95% CIs)	Progressive motility (%) β (95% CIs)	Progressive sperm count (10^6) β (95% CIs)	Total motility (%) β (95% CIs)	Total motile sperm count (10^6) β (95% CIs)
Hot season	TA = 1	−0.035 (−0.061,-0.010)	−0.036 (−0.067,-0.005)	−0.034 (−0.071,0.003)	−0.045 (−0.078,-0.012)	−0.049 (−0.097,-0.000)	−0.040 (−0.072,-0.008)
	TA = 2	−0.089 (−0.158,-0.020)	−0.147 (−0.318,0.025)	−0.056 (−0.162,0.050)	−0.141 (−0.290,0.009)	−0.103 (−0.227,0.022)	−0.102 (−0.231,0.027)
	TA = −1	−0.000 (−0.039,0.038)	−0.015 (−0.056,0.026)	0.017 (−0.013,0.048)	0.002 (−0.044,0.048)	0.018 (−0.026,0.062)	0.001 (−0.050,0.051)
	TA = −2	−0.034 (−0.128,0.061)	−0.016 (−0.099,0.067)	−0.006 (−0.091,0.078)	−0.001 (−0.089,0.088)	−0.005 (−0.112,0.101)	−0.031 (−0.121,0.058)
Cold season	TA = 1	−0.018 (−0.054,0.017)	−0.028 (−0.063,0.007)	−0.009 (−0.042,0.025)	−0.024 (−0.065,0.016)	−0.022 (−0.074,0.031)	−0.036 (−0.082,0.011)
	TA = 2	−0.025 (−0.119,0.068)	−0.047 (−0.133,0.038)	0.004 (−0.098,0.106)	−0.033 (−0.132,0.067)	−0.008 (−0.168,0.152)	−0.058 (−0.175,0.059)
	TA = −3	0.049 (0.011,0.087)	0.048 (0.016,0.080)	0.019 (−0.070,0.108)	0.047 (0.005,0.090)	0.053 (−0.061,0.167)	0.055 (0.013,0.097)
	TA = −6	0.055 (−0.077,0.186)	0.021 (−0.083,0.124)	−0.040 (−0.238,0.159)	0.006 (−0.14,0.152)	−0.025 (−0.294,0.243)	−0.003 (−0.167,0.161)

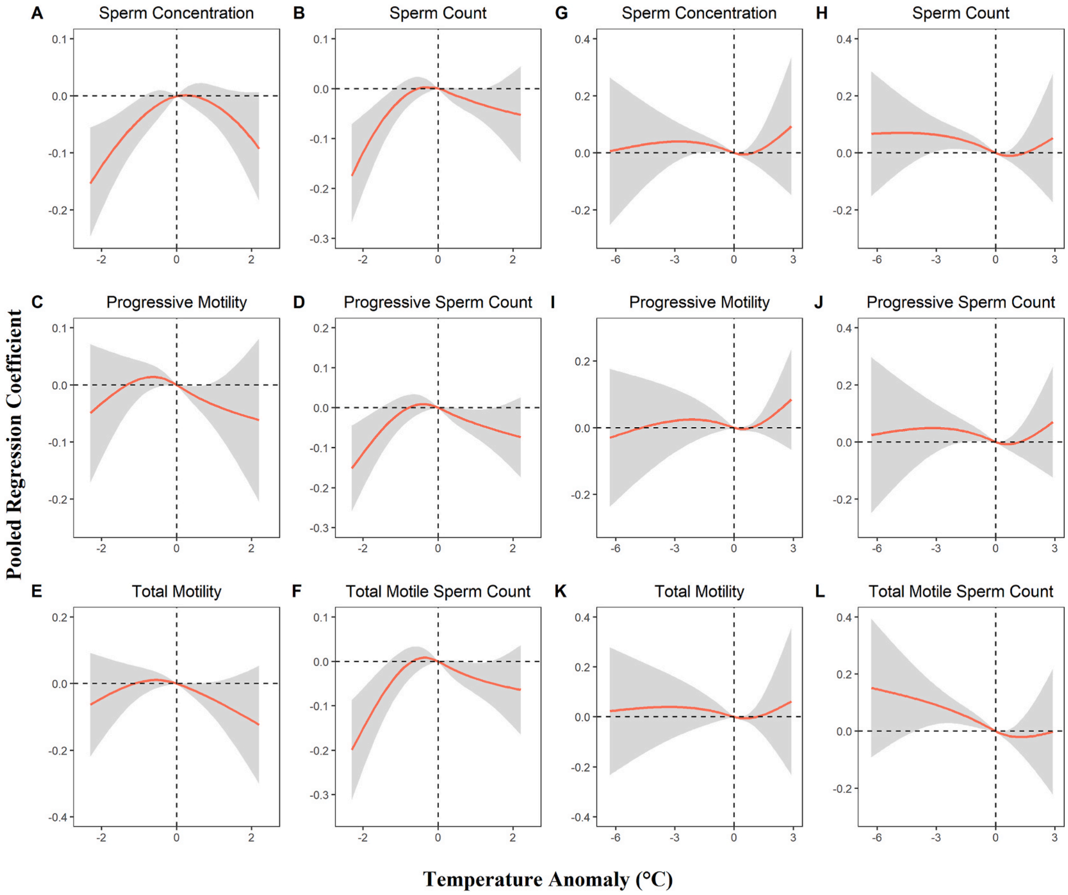

Fig. 3. Sensitivity analysis in subgroup (n = 55,738) of pooled exposure-response relationships between lagged 0–90 days TA and sperm quality by hot and cold seasons during 2014–2020. The regression coefficients (red curves) and corresponding 95% confidence intervals (gray shading) were estimated for temperature anomaly in the hot (A–F) and cold (G–L) seasons. All models were additionally adjusted for the body mass index (BMI), marital status and childbearing history of the subjects. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

temperature in the hot season had adverse effects on sperm concentration, sperm count and total motility sperm count (Figs S11A, S11B and S11F). As shown in Fig. S12, no significant results were observed in the analysis of non-repeated samples, which may be due to the reduction of sample size. According to the occupation of subjects, the data were divided into outdoor and indoor groups for analysis. We found that the sperm quality of outdoor workers was more vulnerable to the adverse effects of anomalous temperature, especially in the hot season (Fig. S13). Additional adjustment of relative humidity did not significantly change the exposure-response relationship between TA and sperm quality (Fig. S14).

3.3. *Subgroup analyses*

As shown in Fig. S15, the results of the subgroup analyses pointed out that heat-related TA per 1 °C increase was significantly negatively associated with sperm concentration (β: 0.044, 95% CI: [−0.079, −0.009]). Fig. 4 presents the pooled estimates of each sperm quality parameter associated with each 1 °C change in TA during the hot and cold seasons, respectively. The heat-related TA per 1 °C increase was significantly negatively associated with sperm concentration (β: 0.055, 95% CI: [−0.100, −0.010]), progressive sperm count (β: 0.043, 95% CI: [−0.077, −0.009]) and total motile sperm count (β: 0.045, 95% CI: [−0.081, −0.009]) during the hot season. In addition, there is also a marginally statistically significant association between heat-related TA per 1 °C increase and decrease in sperm count during the cold season (*P*-value: 0.052). Fig. S16 shows the pooled estimates after additional adjustments for relative humidity. In the hot season, the heat-related TA per 1 °C increase was still significantly negatively associated with sperm concentration, progressive sperm count, and total number of active sperm (all *P*-values <0.05). In addition, the cold-related TA per 1 °C increase was significantly negatively associated with progressive sperm count (β: 0.029, 95% CI: [−0.057, −0.001]) and total motile sperm (β: 0.065, 95% CI: [−0.126, −0.003]) during the cold season. According to the results of separately adjusting for the pollutants SO_2 and O_3 in the model (Figs. S17–S18), we found that the heat-related TA per 1 °C increase was also significantly negatively associated with sperm concentration, progressive sperm count and total motile sperm count in the hot season (all *P*-values

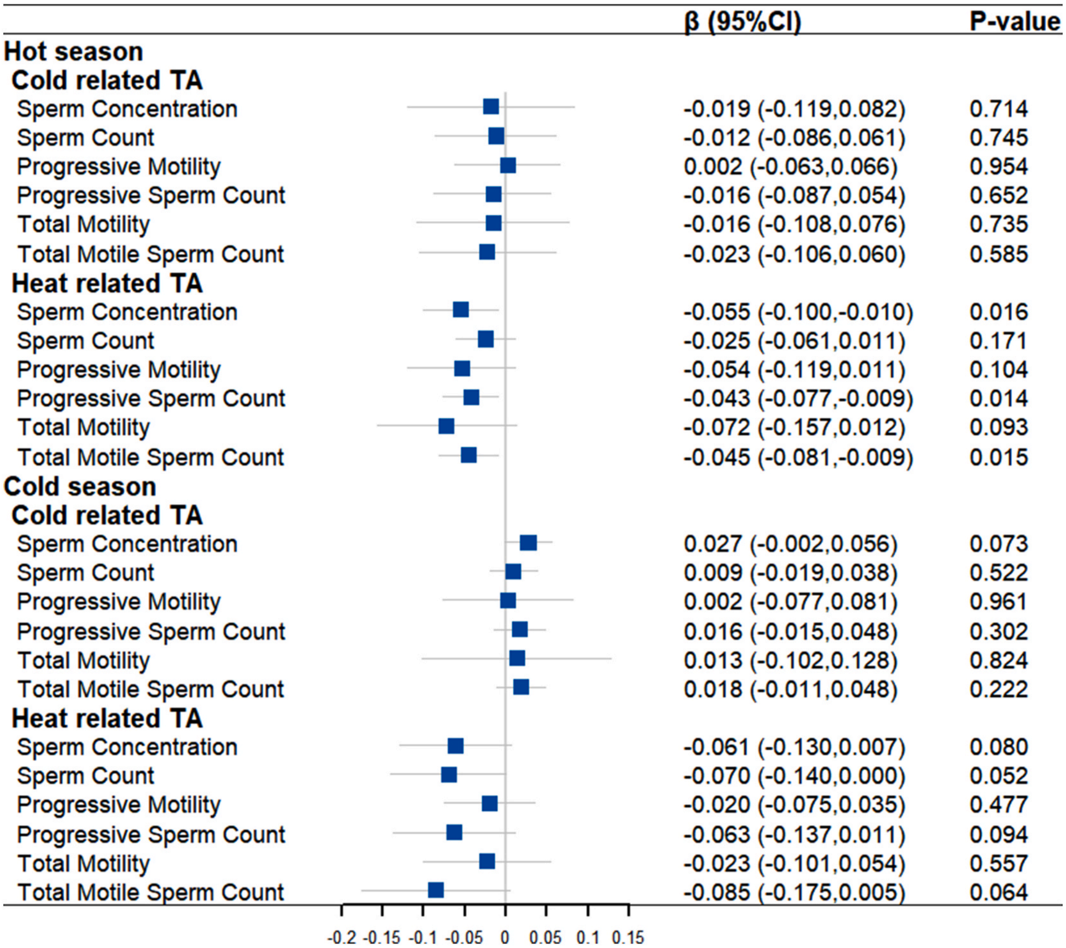

Fig. 4. The pooled association between lagged 0–90 days cold-related TA and heat-related TA and semen quality was estimated by hot and cold seasons.

<0.05). Fig. S19 shows an inverse U-shaped association between TA with a lag of 0–9 days and sperm count. There is a negative association between the anomalous high temperature in the cold season and sperm count (Fig. S19H). The temperature exposures of lagged 10–14 days and 70–90 days in the hot season are still at a high level detrimental to sperm motility (Figs. S20–S21). Anomalous heat for 70–90 days before ejaculation in the hot season was negatively associated with sperm total motility (Fig. S21E).

4. Discussion

This large-scale, multi-center study explored the association between ambient TA and sperm quality in men. We measured the level of anomalously temperature using TA to investigate its effect on male sperm quality pooled from six provinces across China. This study found an inverted U-shaped exposure-response relationship between TA and sperm quality. Particularly during the hot season, ambient temperature that deviate from long-term temperature norm is significantly associated with a decline in sperm quality. In addition, exposure to anomalously heat weather (TA $>$ 0) is significantly associated with the decrease of male sperm concentration, progressive sperm count and total motile sperm count.

Our study investigated the exposure-response relationship between temperature anomalies that deviate from long-term temperatures and sperm quality. No previous studies have adequately considered the heterogeneity of baseline temperatures when exploring temperature effects on sperm quality. A study performed in Italy in 2016 showed a negative association of mean temperature with sperm concentration and sperm count [46]. Another study by Santi et al. showed that seasonal fluctuations in sperm quality were influenced by ambient temperature [6]. However, the above is limited to the study of linear associations. In a study from Wuhan, China, an inverted U-shaped exposure-response relationship between ambient temperature and sperm quality parameters was found, starting from the hypothesis that both high and low temperatures are associated with a decrease in sperm quality [9]. It showed that both above and below temperature thresholds were significantly associated with a decline in sperm quality. Another study from Guangdong Province also indicated that high ambient temperature was negatively associated with semen quality [29]. These findings do not capture the adaptability of the population, but are generally consistent with our result that being above or below a long-term temperature trend can have adverse effects on sperm quality.

Indeed, the mechanisms that effect of temperature on sperm quality remains inconclusive. It is obvious that ambient temperature affects the human skin temperature. Many studies have shown that increased scrotal skin temperature leads to a decrease in ejaculate number and impaired sperm quality [47,48]. Moreover, exposure to heat or cold weather causes acute and chronic stress in humans, and stress increases the level of reactive oxygen species in the male reproductive tract, which adversely affects sperm quality [49]. Several animal studies have demonstrated that the detrimental effects of heat stress on sperm quality may also occur through perturbation of antioxidants that protect sperm from oxidative stress [50,51].

A number of studies have confirmed the association between temperature and spermatozoa [7,52–54]. However, it has been reported that sperm traits can change adaptively in response to changes in temperature [55]. Several animal studies indicated that there may be adaptations in the ability of genotypes associated with sperm traits to be differentially expressed depending on environmental conditions [56,57]. This is an important mechanism for organisms to cope with climate change [58]. David et al. found that drosophila male sterility thresholds are strongly correlated with the thermal tolerance of their species and are influenced by the distribution of climatic zones [59]. Human adaptation varies similarly in geographic distribution, and prolonged exposure induces either heat or cold acclimatization in humans to control the negative health consequences of climate change [27,60]. Therefore, this study used TA as an indicator to take human adaptation based on different climate patterns into account. On this premise, the exposure-response relationship between temperature anomaly and sperm quality during the hot and cold seasons was analyzed separately.

Previous studies have used temperature as a measure of exposure levels in men, obtaining different temperature thresholds across geographic regions [9,29]. Ambient temperatures can vary considerably across geographic regions depending on influences such as climate zones and socioeconomic status [61]. The spatial variation in temperature thresholds may be due to different climatic adaptations in different regions [62,63]. Our study included sperm donors from six regions across China for analysis and found an inverted U-shaped association between TA and sperm quality. An association was found between anomalous temperature weather and decreased sperm quality, with results from a single center and pooled results from multiple centers observed the same temperature pattern (TA = 0) that is most optimal for human sperm health. We also found a significant negative association between anomalous heat (TA > 0 °C) and sperm quality during the hot season, and a significant association between anomalously low temperature (TA < 0 °C) and decreased sperm quality during the cold season.

Global fertility rates have continued to decline over the last two decades [64]. Recent studies have reported that infertility remains a persistent reproductive problem and the global disease burden of infertility has been increasing [65]. Infertility caused by male factors affects approximately 4–6% of couples worldwide, with declining semen quality being a common cause [66]. Accelerating global climate change today, when ambient temperatures exceed critical temperatures, oxidative stress severely affects gonadal function, including impaired mitochondrial function and increased germ cell apoptosis, which leads to decreased male semen quality [67]. Our study demonstrates the inverted U exposure-response curves between TA and sperm quality, confirming the general adverse effects of TA on male sperm quality during the hot season, which has important public health significance. Thus, it is necessary to take appropriate interventions to mitigate the effects of anomalous weather on sperm quality, especially in the hot season. We also found that anomalous heat significantly affects sperm concentration, progressive sperm count, and total motile sperm count. In anomalously heat weather, people should minimize going out and take measures such as air conditioning to cool down. This study provides scientific support for reducing abnormal temperature exposure to preserve good sperm quality.

This study has several strengths. First, the study included a large sample of 78,952 cases from 33,234 subjects which allowed us sufficient statistical power to assess the exposure-response relationship between temperature anomaly and sperm quality. Moreover, subjects in the age range of 19–45 years were also better represented as normal fertile age males [68,69]. Repeated measurements of semen quality also provided an explanation for the within-subject variability. Furthermore, our study included subjects from six provinces in different geographic regions of China, covering part of the temperate, warm-temperate, subtropical, tropical, plateau temperate and plateau sub-cold zones [70]. The results of previous epidemiological studies are limited to the single area studied, and cannot be extended to the climate change risk assessment of other spatial coverage. To capture this effect more accurately, this present study uses TA instead of average temperature by assuming that individuals can adapt to long-term fluctuations in temperature. It enables a better generalizability and representativeness of our findings. Finally, we used a high-resolution data assigned to each subject's residential address, which enabled a more precise individual-level exposure assessment.

Our study also has several limitations. First, although six provinces across China were included in the study, there are still some regions that were not included in the analysis. Therefore, the results of this study should be extended to the whole country with caution. Second, we used 1-km resolution grid data to estimate exposure levels, but data on the activity patterns of subjects and whether they took interventions were lacking, which could lead to misclassification of exposure. Third, this study used TA to account for human adaptation to long-term climate patterns at residential addresses, but ignored the effect of long-term trends. It has been shown that human adaptation to prolonged exposure to heat and cold gradually increases [27,55]. Fourth, the study data lacked some possible confounding factors, including the socioeconomic environment and behavior style (such as using air conditioner or wearing more clothes) of the subjects. Some unobservable confounding factors may also exist. Finally, we lack DNA quality and morphological data of sperm, and future studies should include these covariates in the analysis as much as possible. Future studies will also further consider the effect of apparent temperature.

5. Conclusions

In this multi-center retrospective study, we found an inverted U-shaped exposure response association between temperature anomaly and sperm quality. Even after considering the applicability of long-term temperature in humans, anomalous cold and anomalous heat were negatively associated with sperm quality. Our findings highlight the necessity of reducing anomalous temperature exposure for male reproductive health. It is important to pay attention to the adverse effects of anomalous temperature changes on human sperm quality in the hot season.

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Ethics statement

The study has been reviewed and approved by the Ethics Committee of Guangdong Provincial Reproductive Science Institute, with the approval number: [2021–13]. The study is in line with the Helsinki ethical guidelines. Data used in this work were anonymous, and no individual identifiable information was available in our study.

Data availability statement

Meteorological data are available at https://cds.climate.copernicus.eu. Fine particulate matter data are available at https://weijing-rs.github.io/product.html. The semen sample data used in the study was confidential.

CRediT authorship contribution statement

Lina Xiao: Writing – original draft, Visualization, Validation, Software, Methodology, Formal analysis, Data curation, Conceptualization. **Qiling Wang:** Writing – original draft, Investigation, Data curation. **Haobo Ni:** Writing – original draft, Validation. **Ting Xu:** Writing – original draft, Conceptualization. **Xiaoyan Cai:** Writing – original draft, Validation. **Tingting Dai:** Writing – original draft, Methodology. **Lingxi Wang:** Writing – original draft, Methodology. **Chunying Song:** Writing – review & editing, Investigation. **Yushan Li:** Writing – review & editing, Investigation. **Fuping Li:** Writing – review & editing, Investigation. **Tianqing Meng:** Writing – review & editing, Investigation. **Huiqiang Sheng:** Writing – review & editing, Investigation. **Xiaolin Yu:** Writing – review & editing, Conceptualization. **Qinghui Zeng:** Writing – review & editing, Conceptualization. **Pi Guo:** Writing – review & editing, Project administration, Funding acquisition, Conceptualization. **Xinzong Zhang:** Writing – review & editing, Project administration, Investigation, Data curation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e26765.

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