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Impacts of traffic-related particulate matter pollution on semen quality: A retrospective cohort study relying on the random forest model in a megacity of South China

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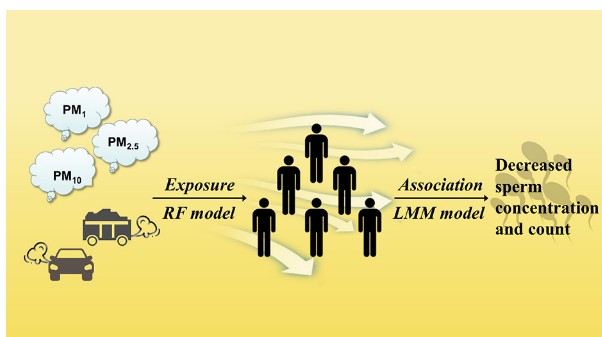
HIGHLIGHTS

- Exposure to traffic-related $PM_{2.5}$ and PM_{10} pollution throughout spermatogenesis may adversely affect semen quality.
- $PM_{2.5}$ and PM_{10} might diminish sperm concentration by mainly affecting the late phase of sperm development.
- Overweight and alcohol consumption may modify the relationships between traffic-related PM pollutants and sperm motility.
- This study provided more evidence for the negative associations between traffic-related PM exposure and semen quality.

GRAPHICAL ABSTRACT



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ABSTRACT

Background: Emerging evidence shows the detrimental impacts of particulate matter (PM) on poor semen quality. High-resolution estimates of PM concentrations are conducive to evaluating accurate associations between traffic-related PM exposure and semen quality.

Methods: In this study, we firstly developed a random forest model incorporating meteorological factors, land-use information, traffic-related variables, and other spatiotemporal predictors to estimate daily traffic-related PM concentrations, including $PM_{2.5}$, PM_{10}, and PM_1. Then we enrolled 1310 semen donors corresponding to 4912 semen samples during the study period from January 1, 2019, and December 31, 2019 in Guangzhou city, China. Linear mixed models were employed to associate individual exposures to traffic-related PM during the entire (0–90 lag days) and key periods (0–37 and 34–77 lag days) with semen quality parameters, including sperm concentration, sperm count, progressive motility and total motility.

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Results: The results showed that decreased sperm concentration was associated with PM_{10} exposures (β: -0.21, 95 % CI: −0.35, −0.07), sperm count was inversely related to both $PM_{2.5}$ (β: -0.19, 95 % CI: −0.35, −0.02) and PM_{10} (β: -0.19, 95 % CI: −0.33, −0.05) during the 0–90 days lag exposure window. Besides, $PM_{2.5}$ and PM_{10} might diminish sperm concentration by mainly affecting the late phase of sperm development (0–37 lag days). Stratified analyses suggested that PBF and drinking seemed to modify the associations between PM exposure and sperm motility. We did not observe any significant associations of PM_1 exposures with semen parameters.

Conclusion: Our results indicate that exposure to traffic-related $PM_{2.5}$ and PM_{10} pollution throughout spermatogenesis may adversely affect semen quality, especially sperm concentration and count. The findings provided more evidence for the negative associations between traffic-related PM exposure and semen quality, highlighting the necessity to reduce ambient air pollution through environmental policy.

1. Introduction

Declining semen quality has been reported over the last decade (Sengupta et al., 2017, 2018). Except for genetic background (Zhao et al., 2022), environmental exposures especially air pollution are one potential factor that contributes to decrements in semen quality. Poor semen quality has been linked to air pollution, including nitrogen oxides, sulfur dioxide, and particulate matter (PM) in vivo studies (Cao et al., 2015; Pires et al., 2011) and epidemiological studies (Huang et al., 2020; Liu et al., 2017; Selevan et al., 2000; Sokol et al., 2006; Wang et al., 2020a; Zhou et al., 2014). Especially, a growing body of literature has shown the detrimental impacts of $PM_{2.5}$ and PM_{10} (aerodynamic diameter <2.5 μm and 10 μm) on semen outcomes (Hammoud et al., 2010; Hansen et al., 2010; Lao et al., 2018; Radwan et al., 2016; Santi et al., 2018; Wu et al., 2017; Zhou et al., 2018). Vehicular traffic is a principal source of air pollutants, of which PM is a possible tracer of traffic emissions and traffic-related pollution (Slama et al., 2007; Yang et al., 2021a). Recent studies have shown that substantial public health benefits can be achieved by controlling traffic-related PM pollution (Zhong et al., 2016), which potentially slows the trend toward deteriorating semen quality.

Hence, accurate estimation of traffic-related PM concentrations plays a crucial part in determining the relationship between PM exposure and semen quality. In general epidemiological studies, the ambient pollution concentration levels of study subjects were implemented by averaging or interpolating from the monitoring stations. However, measurements based on central-site monitors tend to lack sufficient temporal and spatial resolution to capture the spatiotemporal variability of traffic-related air pollutants, resulting in exposure error and biased health impact estimates (Batterman et al., 2020; Hu et al., 2017). To improve the accuracy of exposure assessment, some researches established regression models by incorporating multiple predictors such as satellite remote sensing, meteorological variables, and land use information (Chen et al., 2018; Eeftens et al., 2012). Nonetheless, the parametric models would become increasingly complicated and encounter difficulties when data sets have a mass of predictors and records (Hu et al., 2017). Compared with traditional models, machine-learning (ML) has the capability of fewer restrictive model assumptions and higher computational efficiency. Examples of using ML to estimate PM concentration included Bi and his colleague, who combined the Random Forest (RF) algorithm with CTM forecast product and NASA's GEOS-CF to estimate $PM_{2.5}$ concentration for the next 5 days at a 1 km spatial resolution in central and western provinces of China (Bi et al., 2022). Bozdağ et al. developed artificial neural network (ANN) to estimate PM_{10} concentration in the city of Ankara in Turkey (Bozdağ et al., 2020). Zang et al. proposed a principal component analysis-general regression neural network (PCA-GRNN) to estimate hourly PM_1 (aerodynamic diameter <1 μm) concentrations in China based on Himawari-8 AOD products (Zang et al., 2018). These studies all demonstrated the potential and advantages of using non-parametric ML algorithms to predict pollutant concentrations at high-resolution scales. Therefore, we opted to establish a RF model, a widely used machine learning method that incorporates multiple spatiotemporal variables for estimates of individual exposure concentrations of traffic-related PM.

Most studies considered the pollutant exposures during 0–90 days before semen collection, since sperm development takes approximately 90 days (Ing et al., 2018). Consequently, we estimated the daily traffic-related PM concentrations during 0–90 days prior to the date of ejaculation for comparability. Additionally, two key exposure windows of 34–77 days and 0–37 days prior to semen examinations were both observed to capture the critical development phases of mitosis/meiosis and spermiogenesis (Henry et al., 2021). Overall, in the current study, we developed a ML model incorporating meteorological factors, land-use information, traffic-related variables, and other spatiotemporal predictors to estimate daily concentrations of traffic-related PM, including $PM_{2.5}$, PM_{10}, and PM_1 in Guangzhou - the largest megacity in South China, and further explored the associations between PM exposures and semen quality.

2. Materials and methods

2.1. Semen data

2.1.1. Population

Details of the population inclusion process have been mentioned in our previous study (Wu et al., 2021). In brief, we first recruited semen donors from the Human Sperm Bank of Guangdong province, China, during the study period from January 1, 2019, to December 31, 2019. Then, 4 participants were ruled out since they did not live in Guangdong province for >3 months. Besides, to minimize potential confounding by semen abnormalities unrelated to PM pollution, we excluded 18 men with at least one condition such as mumps, varicocele, prostatitis, kidney disease, and epididymitis/orchitis. Further, 86 sperm donors corresponding to 245 semen samples were excluded, of which 27 samples without semen data and 218 samples had too short (< 2 days) or too long (> 7 days) abstinence period before the date of semen examination. Finally, we included a total of 1310 study subjects living in Guangzhou city (marked as brown dots in Fig. 1a) in the analyses as the “entire group”, corresponding to 4912 semen samples, with most subjects providing multiple semen samples.

2.1.2. Semen quality analysis

Semen collection and analyses were carried out based on our previous reports (Huang et al., 2020; Wu et al., 2021). Briefly, each participant was required to provide semen specimens into designated sterile plastic containers by masturbation in the semen collection room after a self-reported abstinence period of 2–7 days. For each semen sample, we measured several semen quality parameters including sperm concentration ($\times 10^6$/ml), sperm count ($\times 10^6$), progressive motility (%), and total motility (%), and used them (Huang et al., 2020; Wu et al., 2021) as outcome indicators for this study. These four semen parameters are the most common parameters in sperm quality studies, and their definitions can be found elsewhere (Huang et al., 2020; Wu et al., 2021).

The inclusion process of sperm donors, as well as internal and external quality-control procedures of semen collection and analysis, were carried out strictly in accordance with the fifth edition of the WHO laboratory manual for the examination and processing of human semen (World Health Organization, 2010). This study has been approved by the Medical Ethics Committee of Family Planning Special Hospital of Guangdong. All personal information was anonymized, and no data allowing individual identification

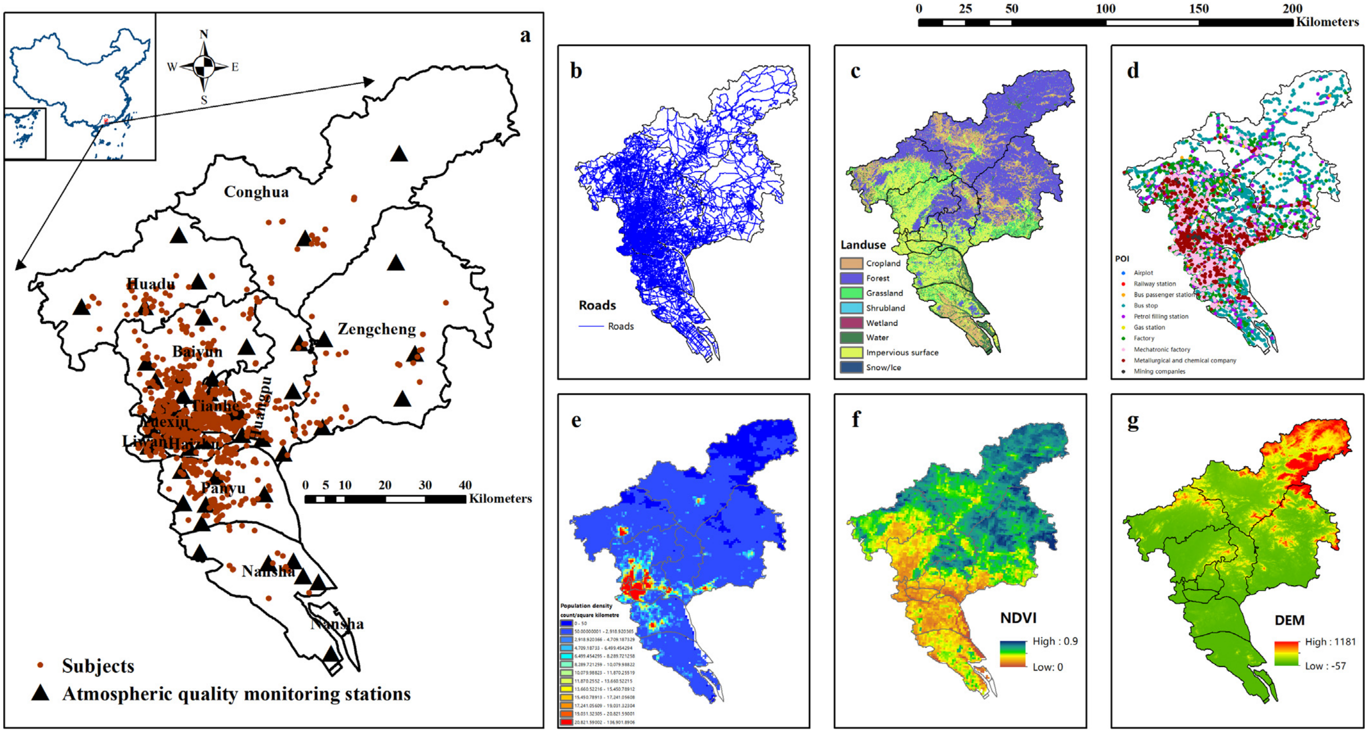

Fig. 1. Geographical distribution of atmospheric quality monitoring stations, study subjects, and geographic information data in Guangzhou, China. (a) The black triangles represent monitoring stations and the brown dots represent study subjects. (b) Road network. (c) Land use. (d) Points of interests (POI). (e) Population density. (f) Normalized differential vegetation index (NDVI). (g) Digital elevation model (DEM). Detailed descriptions of geographic information data are given in Table S1.

was retained. All technicians underwent regular training in laboratory quality control.

2.2. Data set and exposure assessment

2.2.1. Data set

We collected some predictors for concentration modeling and prediction of traffic-related PM, all of which are related to the levels of PM concentration. First, we obtained daily ambient PM data of 51 atmospheric quality monitoring stations (marked as black triangles in Fig. 1a) from Jan 2017 to Dec 2019 from Guangzhou Center for Disease Control and Prevention. In particular, daily PM_1 in situ measurements in the study area were collected from the China Atmosphere Watch Network (CAWNET) of the China Meteorological Administration (Wei et al., 2019). We also collected other spatiotemporal data as model predictors, including meteorological data (daily precipitation, atmospheric pressure, relative humidity, temperature, and wind speed), land-use area data, traffic-related factors (length of roads, distance to the roads, and road density), distance to point of interest (POI), demographic indicators (population density), normalized differential vegetation index (NDVI), digital elevation model (DEM), and other spatial- and temporal-indicators (as shown in Fig. 1b-g). Second, we extracted the longitude and latitude of each monitoring station and the residential address of the study population. The daily meteorological information of each address was interpolated by inverse distance weighting (IDW) based on meteorological data from 86 weather stations in Guangdong province, which have been mentioned in our previous study (Guo et al., 2020). Next, land use and traffic variables were calculated around each site in 10 circular regions with varying radii of 100 m to 5 km as a sum (e.g., length of road) within each buffer. We obtained population density, NDVI, and DEM values by extracting the raster data values of the grid where the addresses are located. Annual and monthly variables (e.g. population density and NDVI) were linked with daily predictors based on the calendar year or month in which they were collected, as the values of those variables are unlikely to change over one year or month, respectively (Chen et al., 2018). See Table S1 in Supplementary Information for more details on spatiotemporal data.

2.2.2. Random forest model

Random forest is one of the most common models of ML algorithms and was firstly proposed by Breiman (Breiman, 2001). The algorithm of RF is to construct a set of decision trees by bootstrapping (random resampling with replacement) from the original data, and then use the best split for each node according to a subset of randomly chosen predictors at each node. The final predictions are obtained by aggregating the predictions of all trees. Two user-defined parameters, including the number of trees (n_{tree}) and the number of predictors randomly chosen to split at each node (m_{try}), are optimized by maximizing the coefficient of determination (R^2) computed on out-of-bag (OOB, the data not used in bootstrap sample).

2.2.3. Assessment of traffic-related PM exposure by RF model

We used the RF model to assess the daily concentration of traffic-related PM exposure, including $PM_{2.5}$, PM_{10}, and PM_1. The schematic diagram of the development of RF model was shown in Fig. 2. First, we developed three separate RF models with a set of the most reasonable and optimal parameters (n_{tree} and m_{try}) for each pollutant respectively by incorporating the ground-based PM concentrations and the above-prepared predictors of all atmospheric quality monitoring stations. Then, 10-fold cross-validation (CV) was applied to evaluate the performance of RF models. We calculated the determination coefficient (R^2) and root mean squared error (RMSE) between measured data and CV predicted data to evaluate the prediction accuracy of models. After model validation, the spatiotemporal predictors retrieved from each address of the study population were input into the constructed optimal model to predict the daily traffic-related PM concentrations within the exposure windows. Finally, we calculated the median of PM concentrations during exposure periods as individual exposure levels, since the distributions of PM exposures within exposure windows generally do not follow normal distributions.

2.3. Statistical analysis

We employed linear mixed models (LMM) to associate individual exposures to $PM_{2.5}$, PM_{10}, and PM_1 during the entire (0–90 lag days) and key

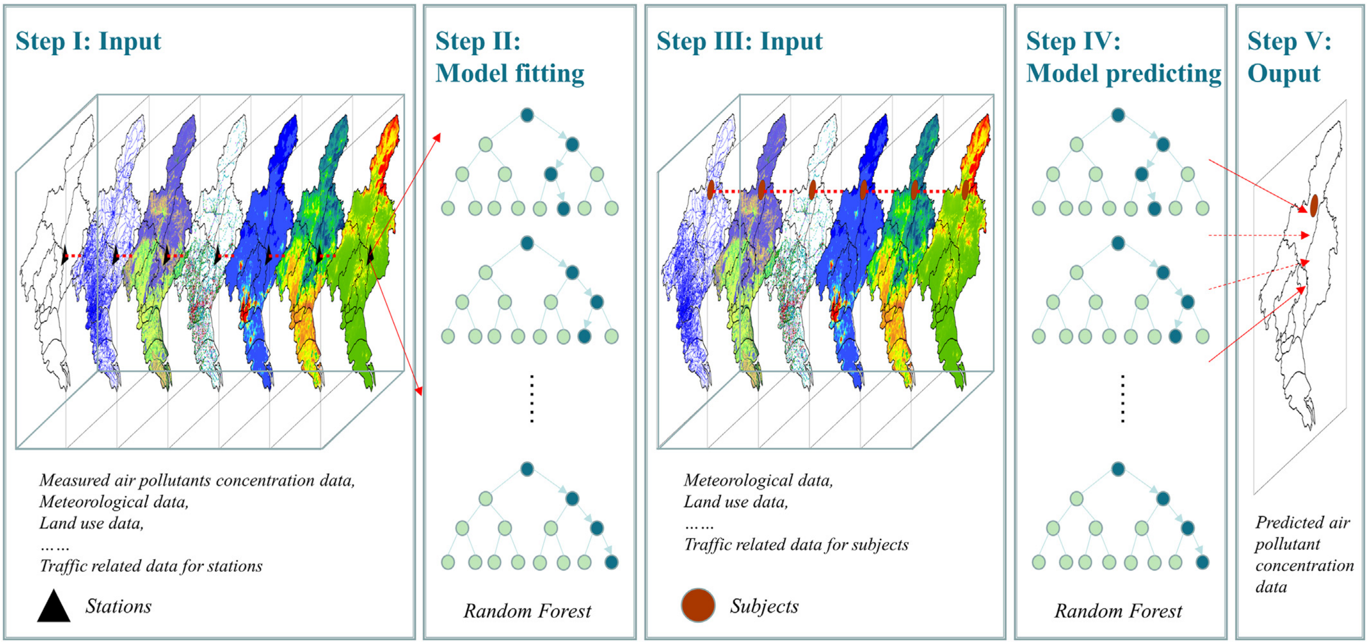

Fig. 2. Schematic diagram for assessing traffic-related PM exposure by RF model.

periods (0–37 and 34–77 lag days) with semen quality parameters, including sperm concentration, sperm count, progressive motility and total motility. Due to the skewed distribution of semen quality parameters, the BoxCox transformation method was implemented to ensure the outcome measures were satisfied or approximately satisfied with normal distributions. All semen quality parameters were standardized for better interpretation and comparison. Therefore, both the standardized deviation (SD) and the variance were equal to 1, so the regression coefficients provided estimates of the impacts of PM exposure based on a change in SD of the outcome measures, and it is easier to compare (Wu et al., 2017).

To account for correlations between repeated semen samples from the same subject (Wu et al., 2017), multivariate linear mixed models with subject-specific random intercept were established to investigate the impacts of traffic-related PM exposure on sperm quality. All models were adjusted for age, body mass index (BMI), percent body fat (PBF), ethnic, education, marital status, childbearing history, career, smoking status before donation, drinking status one week before donation, abstinence period, and month at semen examination. Based on previous literature demonstrating nonlinear associations between ambient temperature and semen quality, the average temperature during the entire and key periods was also adjusted in models by using a natural cubic spline function with degrees of freedom (*df*) of 3.

We estimated regression coefficients with 95 % confidence intervals (CI) for each semen quality parameter associated with per interquartile range (IQR) increase of each PM exposure at three different key periods. In addition to the single-pollutant model, we also employed two-pollutants models to account for potential confounding effects of other pollutants. Besides, we also split the PM exposure into quartiles (Q1 to Q4) based on its distribution among the semen samples, and estimated the regression coefficients with the first quartile as the reference level. The linear trend across quartiles was tested by using the medians within each quartile range as continuous variables in the model. In addition, we conducted exposure-response analyses stratified by average temperature (or say, season) during 0–90 days before semen examination to better understand the effect of temperature on the associations between PM exposure and semen quality. Based on the median temperature (24.6 °C), the subjects were stratified into two groups: Low-temp (≤ 24.6 °C) and High-temp (> 24.6 °C). Furthermore, we constructed stratified models to evaluate effect modifications by potential modifiers (age, PBF, smoking, and drinking) on the association between PM exposure and sperm quality. These variables were stratified as age (< 30 and ≥ 30 years old), PBF (< 25 and ≥ 25 %), smoking (no and yes), and drinking (no and yes). The effect modifications were examined on the multiplicative scale by adding interaction terms between pollutants and modifiers in each separate model, with the significance tested via the likelihood ratio test (Xu et al., 2021).

Sensitivity analyses were conducted to test the robustness of our results. Since poor semen quality may be ascribed to abnormalities unrelated to traffic-related PM exposure, we focused on the study subjects with normal semen quality and considered them as a subgroup for sensitively analyses. The subgroup excluded subjects with lower reference limits for semen characteristics according to WHO standard (WHO, 2010): sperm concentration $< 15 \times 10^6$/mL, sperm count $<39 \times 10^6$, total motility <40 % or progressive motility <32 %. Then, we repeated the above data analyses based on subgroup samples. All geospatial analyses were performed using ArcGIS version 10.6. RF, LMM, and other statistical analyses were performed with R version 4.0.2. All the tests were two-sided and $P < 0.05$ was considered statistically significant.

3. Results

Fig. 3 presented the performances of RF in model-fitting and sample-based 10-fold CV. The model-fitting R^2 values of $PM_{2.5}$, PM_{10}, and PM_1 were 0.86, 0.85, and 0.72, with corresponding RMSE of 6.69, 11.09, and 9.66 μg/m^3, respectively. The RF model validation has similar characteristics. The predicted PM_1 concentrations displayed reasonable agreement with the ground-monitored PM_1 data, but with a smaller R^2 of 0.72, which may be due to fewer training data samples.

Table 1 summarized the characteristics of semen donors. The entire group included 1310 study subjects with 4912 samples. Most of the study population were younger than 30 years old (81.8 %), and the number of Han ethnic was far exceeded that of other ethnic groups. Among these subjects, over 80 % had a college degree or higher, 83.6 % were unmarried, and 87.4 % had no children. Only 14.0 % of the subjects drank alcohol a week before donation, and approximately 80 % did not smoke. The median levels of sperm concentration, sperm count, progressive motility, and total motility were 72.00×10^6/mL, 255.0×10^6, 58.00 %, and 60.00 %, respectively. We also summarized the characteristics of subjects in the subgroup (Table 1). The subgroup involved 1204 subjects with 4672 samples, and there was no statistically significant difference across the entire group and subgroup for demographic characteristics (all *P*-value >0.05). After excluding

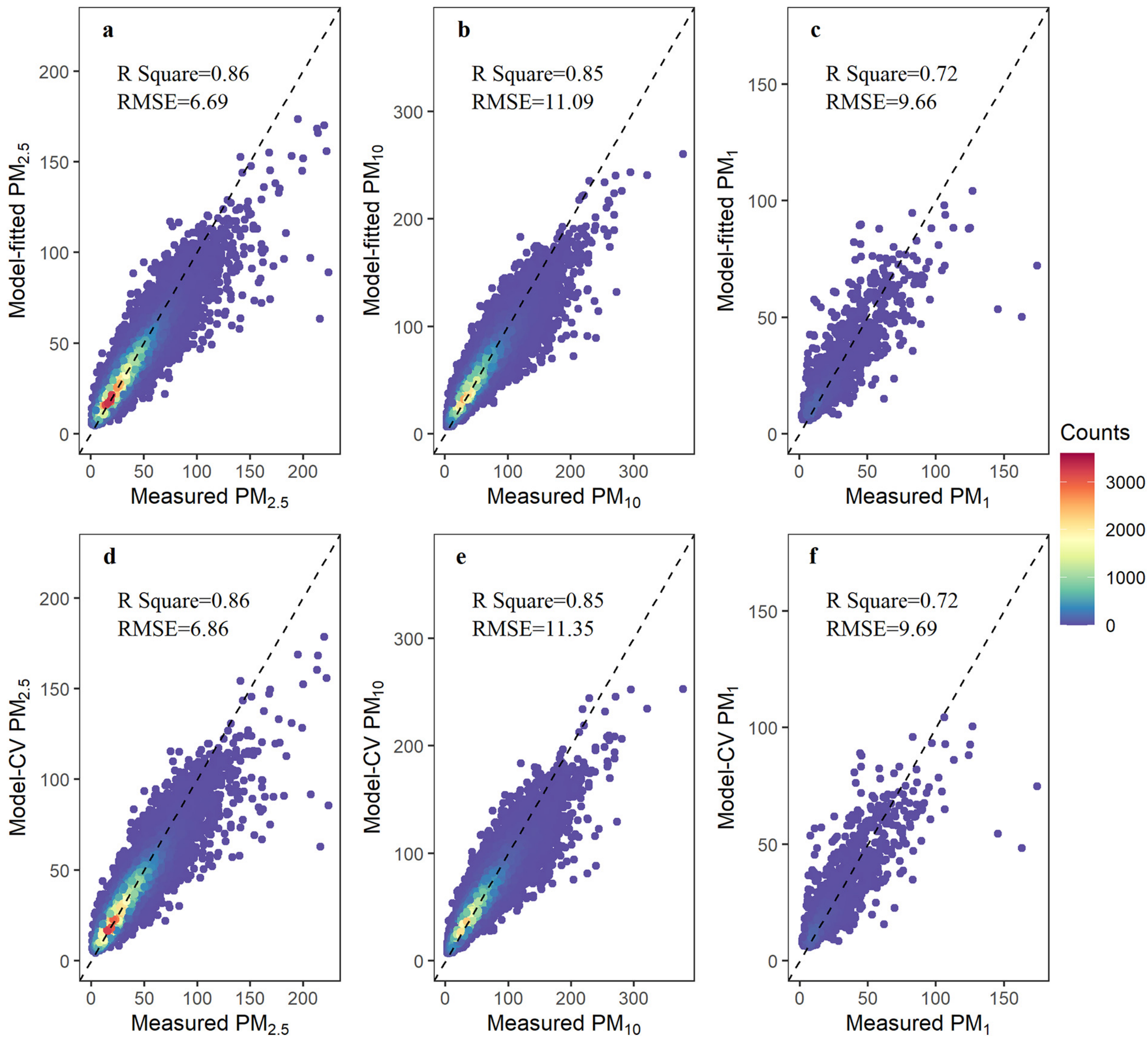

Fig. 3. Density scatterplots of model-fitting results (a to c) and sample-based 10-fold cross-validation results (d to f) from the RF model (unit: μg/m^3). The black dashed lines represent the 1:1 line. RMSE: root mean square error.

subjects with abnormal semen characteristics, the semen parameters of the subgroup were slightly higher than those of the entire group (with *P*-value <0.05). The distribution of traffic-related PM exposure and the Spearman's rank correlation coefficients between PM exposure were presented in Table 2. Obviously, $PM_{2.5}$ exposure was strongly positively correlated with PM_{10} ($r_s = 0.93$).

The associations between traffic-related PM exposure and sperm quality in both single- and two- pollutant models were displayed in Fig. 4. In single-pollutant model, negative associations of sperm concentration with PM_{10} (β: -0.21, 95 % CI: −0.35, −0.07), sperm count with $PM_{2.5}$ (β: -0.19, 95 % CI: −0.35, −0.02) and PM_{10} (β: -0.19, 95 % CI: −0.33, −0.05) were observed for all subjects in entire group. In two-pollutant models, $PM_{2.5}$ and PM_{10} were not included in the same model due to their high correlation, which would result in serious multicollinearity (variance inflation factor > 10). Overall, the results yielded consistent negative associations between PM exposure and sperm concentration and count after further adjusting for other pollutants in the two-pollutant models. For subgroup analyses, we also observed similar associations among subjects with normal semen quality parameters.

We further examined the relationships between traffic-related PM exposure and sperm parameters during two key periods of spermatogenesis (Fig. 5). In late spermatogenesis (0–37 lag days), we only identified that decreased sperm concentration was associated with per IQR increase in $PM_{2.5}$ (β: -0.15, 95 % CI: −0.28, −0.01) and PM_{10} (β: -0.17, 95 % CI: −0.31, −0.03) in the entire group, and the associations still remained significant in the subgroup. In contrast, PM exposures in early spermatogenesis (34–77 lag days) were not related to any semen quality parameter both in the entire group and subgroup (all *P*-value >0.05). Fig. 6 demonstrated the shape of exposure-response of semen parameters associated with quartiles of PM pollutants. Sperm concentration decreased nonlinearly across PM_{10} quartiles (*P*-value for linear trend = 0.04, not shown in Fig. 6), while sperm count was only inversely associated with PM_{10} exposure at the middle quartiles (Q2 and Q3). There were no significant associations observed for sperm motility across the quartiles of PM exposure. The results for subgroup analysis were consistent with those of the all study population.

In the results of the stratified analysis by temperature shown in Fig. S1, we observed that for temperature ≤ 24.6 °C, PM_{10} exposure was associated with decreased sperm concentration (β: -0.18, 95 % CI: −0.33, −0.02) and count (β: -0.16, 95 % CI: −0.32, −0.01) in entire group. While for temperature > 24.6 °C, negative associations between $PM_{2.5}$ and PM_{10} exposures and sperm motility were found. Similar associations still remained significant in the subgroup.

As shown in Table S2, there were statistically significant effect modifications between PM_1 exposure and sperm concentration in different age

Table 1
Characteristics of study subjects during 0–90 days before the date of semen examination.

Variables	number (%) / median [IQR]		*P*-value*
	Entire group	Subgroup[a]	
Total subjects	1310	1204	
Total samples	4912	4672	
Age, years			0.750
<30	4019 (81.8)	3842 (82.2)	
30–39	838 (17.1)	784 (16.8)	
≥40	55 (1.1)	46 (1.0)	
BMI, kg/m^2			0.986
<18.5	525 (10.7)	501 (10.7)	
18.5–23.9	3129 (63.7)	2980 (63.8)	
24.0–27.9	994 (20.2)	948 (20.3)	
≥28	264 (5.4)	243 (5.2)	
PBF, %			0.719
<25	4052 (82.5)	3868 (82.8)	
≥25	860 (17.5)	804 (17.2)	
Education			0.788
College and higher	4324 (88.0)	4122 (88.2)	
High school and lower	588 (12.0)	550 (11.8)	
Ethnic			0.909
Others	165 (3.4)	154 (3.3)	
Han	4747 (96.6)	4518 (96.7)	
Marital status			0.983
Unmarried	4108 (83.6)	3910 (83.7)	
Married	741 (15.1)	704 (15.1)	
Divorced	63 (1.3)	58 (1.2)	
Childbearing history			0.830
Childless	4293 (87.4)	4091 (87.6)	
With children	619 (12.6)	581 (12.4)	
Career			1.000
Salesman	566 (11.5)	540 (11.6)	
Computer	455 (9.3)	421 (9.0)	
Service	121 (2.5)	117 (2.5)	
Unemployed	383 (7.8)	370 (7.9)	
Driver	13 (0.3)	12 (0.3)	
Businessman	49 (1.0)	45 (1.0)	
Worker	103 (2.1)	99 (2.1)	
Company employee	871 (17.7)	822 (17.6)	
Chef	9 (0.2)	9 (0.2)	
Student	1833 (37.3)	1757 (37.6)	
Teacher or doctor	171 (3.5)	161 (3.4)	
Soldier or police	33 (0.7)	31 (0.7)	
Others	305 (6.2)	288 (6.2)	
Smoking			0.692
No	3912 (79.6)	3737 (80.0)	
Yes	1000 (20.4)	935 (20.0)	
Drinking			0.961
No	4224 (86.0)	4015 (85.9)	
Yes	688 (14.0)	657 (14.1)	
Abstinence period, days			0.745
2–3	1457 (29.7)	1386 (29.7)	
4–5	2735 (55.7)	2626 (56.2)	
6–7	720 (14.7)	660 (14.1)	
Sperm parameters			
Sperm concentration, 10^6/ml	72.00 [52.00, 95.00]	73.00 [54.00, 96.00]	0.002
Sperm count, 10^6	255.00 [176.23, 348.00]	261.80 [186.00, 353.52]	0.001
Progressive motility, %	58.00 [50.00, 64.00]	58.00 [52.00, 64.00]	0.021
Total motility, %	60.00 [53.00, 66.00]	61.00 [55.00, 66.00]	0.022

Abbreviations: BMI: body mass index. PBF: percent body fat. SD: standard deviation.
[a] Subgroup: The subgroup only included subjects with normal sperm concentration, sperm count, and motility according to the WHO reference levels for human semen parameters.
* *P*-value was calculated by chi-square test or Kruskal-Wallis test.

groups (*P*-value for effect modification = 0.02). Meanwhile, we found the associations between PM_{10} and sperm motility (both progressive motility and total motility) were modified by drinking (both *P*-value for effect modification <0.05). There were no significant interactions between PBF, smoking category and risk of outcomes. Regarding the subgroup shown in Table S3, the effect modification of PBF existed on the associations between

Table 2
Distribution of traffic-related PM pollutant exposures during 0–90 days before the date of semen examination of the study subjects and their Spearman correlation coefficient.

	Air pollutant	Mean	SD	Median	IQR	$PM_{2.5}$	PM_{10}	PM_1
Entire group	$PM_{2.5}$	28.61	6.64	28.57	10.81	1.00	0.93	0.35
	PM_{10}	49.09	11.41	47.15	17.47		1.00	0.30
	PM_1	24.77	5.24	24.71	7.38			1.00
Subgroup[a]	$PM_{2.5}$	28.62	6.63	28.60	10.78	1.00	0.93	0.34
	PM_{10}	49.13	11.42	47.16	17.50		1.00	0.29
	PM_1	24.78	5.25	24.73	7.38			1.00

Abbreviations: SD: standard deviation. IQR: interquartile range.
[a] Subgroup: The subgroup only included subjects with normal sperm concentration, sperm count, and motility according to the WHO reference levels for human semen parameters.

$PM_{2.5}$ and PM_{10} and sperm motility (all *P*-value for effect modification <0.05), even though the stratified effects of those pollutants were non-significant. Results for effect modification by drinking remained statistically significant. We also observed varying relationships between PM exposure and semen quality across some modifiers even though the effect modifications were not identified. For instance, stratified analyses based on alcohol consumption revealed that participants who drank alcohol a week prior to donation had a higher risk (β: -0.52, 95 % CI: −0.89, −0.16) of declining sperm concentrations for per IQR increase in PM_{10} exposure when compared to participants who never drink (β: -0.21, 95 % CI: −0.37, −0.05) (*P*-value for effect modification >0.05).

4. Discussion

In this study, we incorporated spatiotemporal data and random forest algorithms to predict traffic-related PM concentrations among 1310 men from Guangzhou, China during different periods of sperm development and evaluated the potential associations between traffic-related PM exposures and semen quality by using linear mixed models. The results showed that decreased sperm concentration was associated with PM_{10} exposures and sperm count was inversely related to both $PM_{2.5}$ and PM_{10} during the 0–90 days lag exposure window both in using single- and two- pollutant models. Moreover, the associations during the 0–37 lag days indicated that $PM_{2.5}$ and PM_{10} might diminish sperm concentration by mainly affecting the late phase of sperm development. The results based on subgroup analysis suggested that the negative associations persisted among the participants with normal semen parameters. Further stratified models demonstrated the robustness of the associations between the exposure to $PM_{2.5}$ and PM_{10} and semen quality. In particular, PBF and drinking seem to modify the associations between PM exposure and sperm motility. We did not observe any significant associations of PM_1 exposures with semen parameters.

The results of our study are comparable to those of previous studies where the associations for $PM_{2.5}$, PM_{10} and sperm concentration, sperm count have been also observed. For instance, among 3797 semen samples from Guangdong province, China, the average $PM_{2.5}$ (β:-0.29, 95 % CI: −0.54, −0.04) and PM_{10} (β:-0.25, 95 % CI: −0.44, −0.05) throughout the entire 90 days of sperm development were correlated with decreased sperm count (Huang et al., 2020). Wu et al. also reported that sperm concentration and count were inversely related to the 90-day mean concentration of $PM_{2.5}$ and PM_{10} among 1759 men in Wuhan (Wu et al., 2017). However, inconsistent results were also reported. Two studies conducted in the United States and one study in China did not identify any associations similar to ours (Hansen et al., 2010; Nobles et al., 2018; Zhao et al., 2022).

Those inconsistencies might be derived from several reasons. First, constituents and concentrations of ambient PM exposure are variant in each study area, leading to differential toxicities and health effects (Bell et al., 2007). The average concentration levels of $PM_{2.5}$ and PM_{10} observed in our study were 28.61 and 49.09 μg/m^3, respectively, which were approximately two times higher than those in Hansen's study (range from 10.9 to 14.2 μg/m^3 across three counties for $PM_{2.5}$) and Nobles's study (12.2 μg/m^3 for

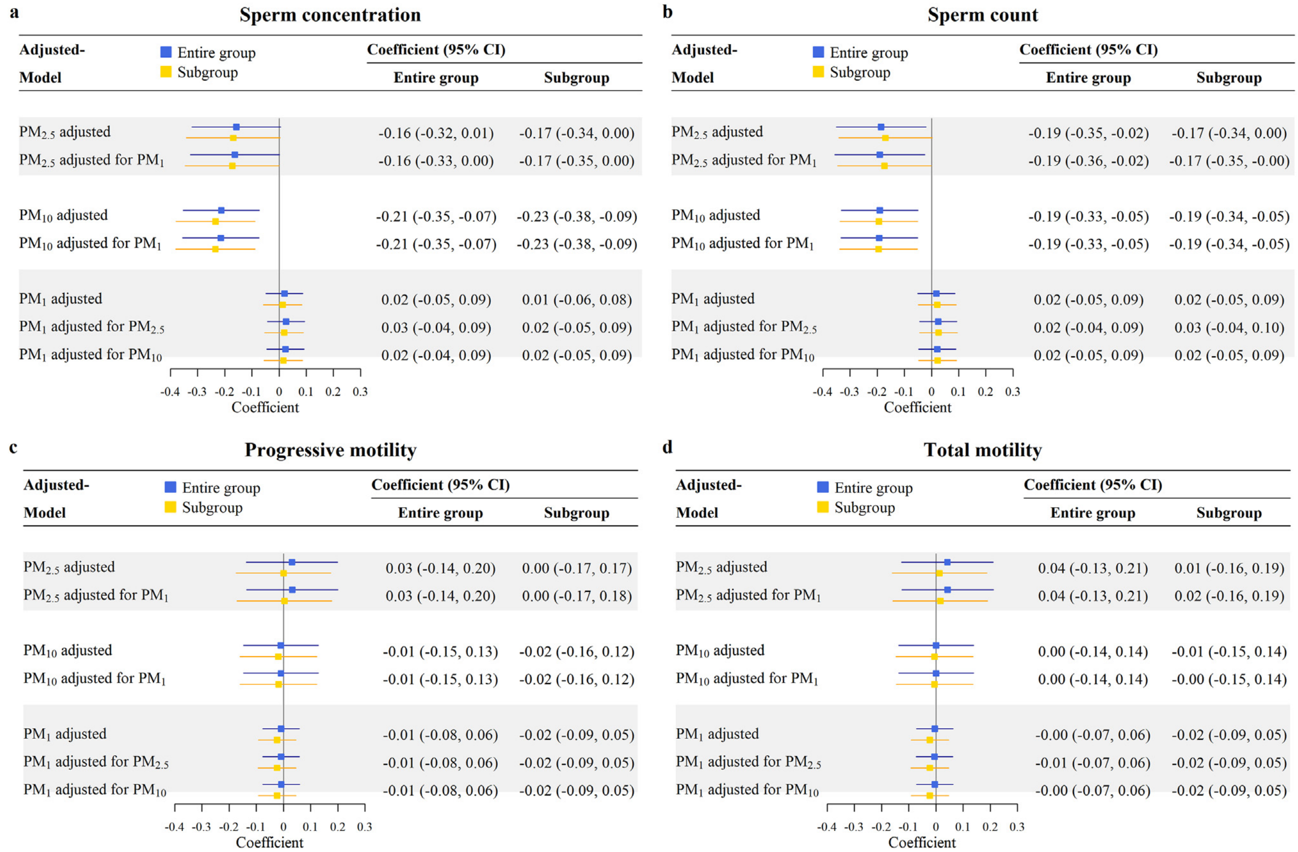

Fig. 4. Regression coefficients and 95 % confidence intervals (CIs) of semen parameters (a. Sperm concentration. b. Sperm count. c. Progressive motility. d. Total motility.) associated with each interquartile range (IQR) increases of pollutant ($PM_{2.5}$, PM_{10}, PM_1) exposures at 0–90 days before the date of semen examination in single- and two-pollutant models. Single-pollutant models were adjusted for age, BMI, PBF, education, ethnic, marital status, childbearing history, career, smoking, drinking, abstinence period, month and a natural cubic spline function of temperature during exposure period ($df = 3$). Two-pollutant models were adjusted for the same covariates as the single-pollutant models, and also adjusted for the other pollutant shown above. The subgroup only included subjects with normal sperm concentration, sperm count, and motility according to the WHO reference levels for human semen parameters.

$PM_{2.5}$ and 24.4 μg/m^3 for PM_{10}) (Hansen et al., 2010; Nobles et al., 2018). In contrast to our findings, neither study found significant associations between PM exposures and sperm concentration and count. On the other hand, levels of $PM_{2.5}$ and PM_{10} of our observed median values of 28.57 and 47.15 μg/m^3 were lower than those of two studies conducted in China, with corresponding median values in 66.2 and 104.0 μg/m^3 in Wuhan (Wu et al., 2017), and 43.4 and 81.1 μg/m^3 in Huai'an (Guan et al., 2020). Both studies showed consistent links between PM exposures throughout entire spermatogenesis and the declines in sperm count and sperm concentration. Given these previous researches, the association between air pollution and semen quality may have a threshold effect that is difficult to detect when pollutant concentration levels are low (Nobles et al., 2018). Second, exposure assessment approaches resulted in differential individual levels of PM concentration. Compared to IDW or RF (Ma et al., 2022; Yang et al., 2021b), the application of the nearest monitoring station or the city-wide average (Qiu et al., 2020; Zhao et al., 2022) would disguise the spatial variations in pollutants so that have limitations to estimating accurate daily concentrations for the participants. Third, differences across populations and selection bias in different studies would also affect associations.

We selected two more targeted exposure windows (0–37 and 34–77 lag days) in this study to assess the impacts of traffic-related PM pollution on spermiogenesis. The duration of spermiogenesis consumes approximately 74 days (Amann, 2008; Heller and Clermont, 1963, 1964), hence we took the median value as the cut-off point for staging and added 3-days buffers to account for possible variability (Henry et al., 2021). The results showed that decreased sperm concentration was associated with per IQR increase in $PM_{2.5}$ and PM_{10} in late spermatogenesis (0–37 lag days), whereas null associations were found in early-phase (34–77 lag days). The late phase involves a process of spermatogenesis, spermiogenesis, namely the transformation of a spherical spermatid to a spermlike mature spermatid (Amann, 2008). Evidence from animal studies has shown that other pollutants such as bisphenol A can interfere with spermiogenesis by impairing sperm DNA integrity (Pan et al., 2020). Therefore, we infer that PM also impairs spermiogenesis by disrupting sperm DNA. Compared to Henry's team where similar exposure windows also were applied, they found protective effects of PM on sperm concentration (OR = 0.35 for $PM_{2.5}$, OR = 0.28 for PM_{10}) in the late-phase and inverse associations between $PM_{2.5}$ and total abnormal head parameters (OR: 1.52, 95 % CI: 1.04–2.32) in the early-phase. However, it is hard to directly compare those results in corresponding key periods because Henry et al. converted semen parameters to dichotomous variables rather than continuous variables (Henry et al., 2021). The other study conducted by Nobles was also based on a 72-day spermatogenesis period, but he used smaller 15-day windows (0–14, 15–29, 30–44, 45–59, and 60–72 days prior to ejaculation) to identify specific periods (Nobles et al., 2018). Even though some literature found negative relationships between PM and sperm concentration in the relatively middle or late period (Guan et al., 2020; Ma et al., 2022), the application of different lags complicates the comparison of results across studies.

The biological mechanisms underlying the link between traffic-related PM exposure and impaired semen quality remains to be determined. Several potential hypotheses have been proposed, including oxidative stress mechanisms, inflammatory reactions, endocrine disruption, and so on. Oxidative stress induced by $PM_{2.5}$ or PM_{10} was the most reported assumption to account for the sperm dysfunction. PM exposure was associated with excess reactive oxygen species, which results in disruption of the blood-testis barrier, triggering apoptosis and autophagy, impairing mitochondria structures, thereby

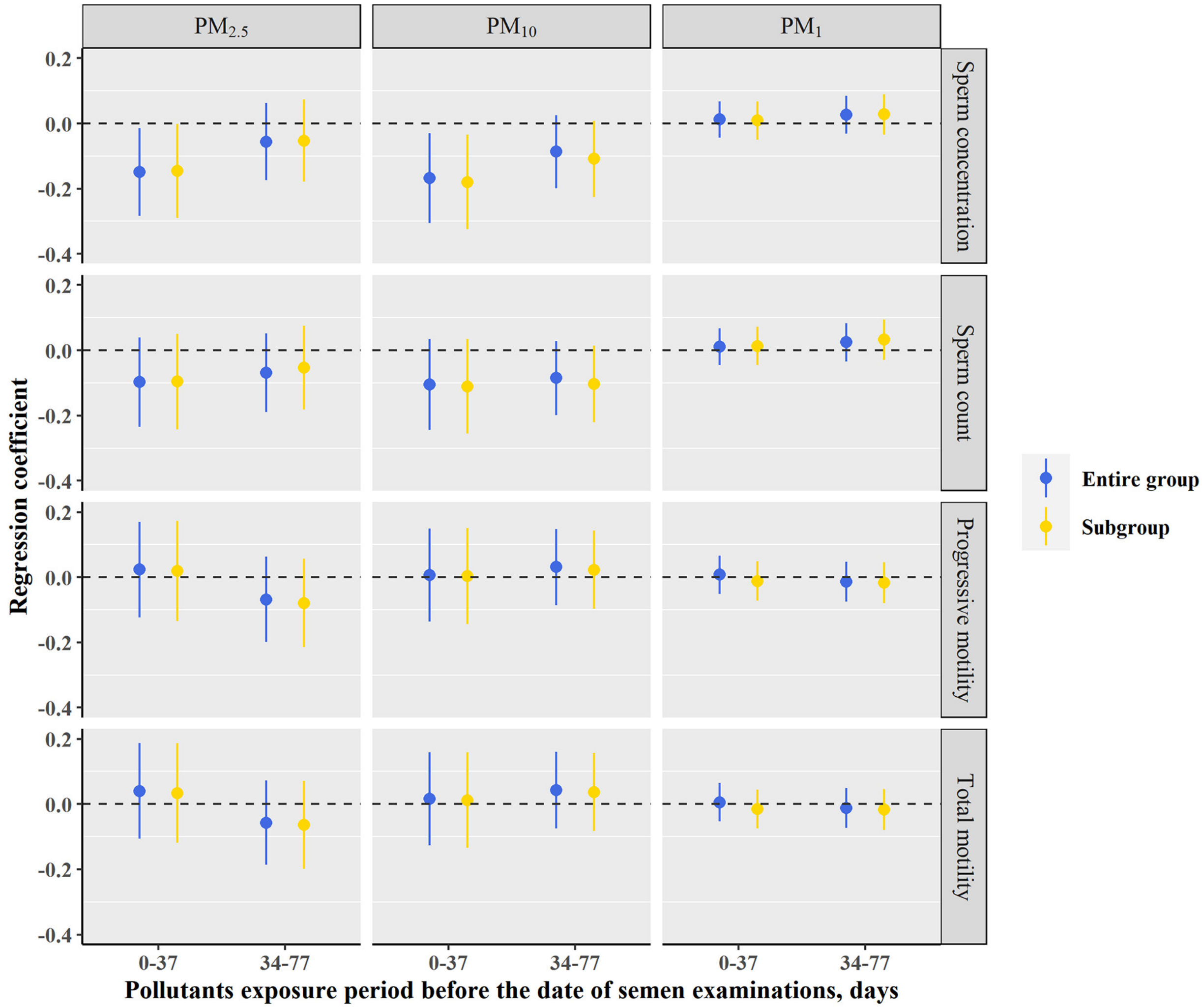

Fig. 5. Regression coefficients and 95 % confidence intervals (CIs) of semen parameters associated with each interquartile range (IQR) increases of pollutant ($PM_{2.5}$, PM_{10}, PM_1) exposures at 0–37 and 34–77 days before the date of semen examination. The models were adjusted for age, BMI, PBF, education, ethnic, marital status, childbearing history, career, smoking, drinking, abstinence period, month and a natural cubic spline function of temperature during exposure period ($df = 3$). The subgroup only included subjects with normal sperm concentration, sperm count, and motility according to the WHO reference levels for human semen parameters.

decreasing semen quality (Cao et al., 2015; Wei et al., 2018; Zhang et al., 2018). Evidence from animal models also demonstrated that the decline in sperm quality may partly be caused by the PM-induced inflammatory reaction in the testes (Li et al., 2017; Zhou et al., 2019). Besides, ambient PM contains diverse toxic chemical components such as polycyclic aromatic hydrocarbons (PAHs), which have been revealed that be correlated with sperm DNA damage (Han et al., 2011; Ma et al., 2019). Meanwhile, PAHs could also work as hormone disruptors to affect the hypothalamic-pituitary-gonadal axis and testicular spermatogenesis (Jeng and Yu, 2008; Qiu et al., 2018). Overall, long-term exposure to PM may damage the testicular function and subsequently affect spermatogenesis, leading to reduced sperm concentration and count. Further toxicity experiments are required to elucidate the underlying mechanisms.

By stratifying study subjects by temperature, we found that PM_{10} remained related to sperm concentration and count at relatively low temperature, which was consistent with the results of a study conducted in Wuhan, China (Wu et al., 2017). In addition, when in higher temperature, both progressive and total motility were significantly associated with $PM_{2.5}$ and PM_{10}. Studies have shown that decreased sperm quality was induced by high temperature by disrupting the integrity of DNA in sperm cells or over-expression of heat shock proteins (Wang et al., 2020b). Considering the synergistic impact of ambient temperature and air pollution on health outcomes, future research could focus on the effect of the interaction between temperature and air pollution on sperm quality.

Our findings also implied possible and slight effect modifications of alcohol consumption and overweight on the relationships between PM pollutants and semen quality. As shown in Table S2, the observed associations between $PM_{2.5}$ and PM_{10} and sperm count and concentration almost remained statistically significant among stratified analyses of different factors, with null effect modifications (P-value ranges from 0.21 to 0.94), indicating that these impacts were reliable among different populations. As shown in Table S2 and S3, significant modification effects of PBF and drinking factors were majorly observed in the associations between PM and sperm motility (including progressive motility and total motility) (e.g. drinking modify the association between PM_{10} and total motility with P-value $= 0.02$), suggesting that sperm motility in people who are overweight or drinking alcohol might be more susceptible to traffic-related PM pollution. One potential pathway of how overweight could modify the associations is through mitochondrial damage. Studies have shown that both increased BMI and oxidative stress were associated with worsened mitochondrial damage in spermatozoa (Oliveira et al., 2018; Zhang et al., 2018). Therefore, we speculated that obesity may aggravate the abnormalities in mitochondrial structure caused by oxidative stress, resulting in energy metabolism disorder, and thus reduced sperm motility. Even though few associations between PM and

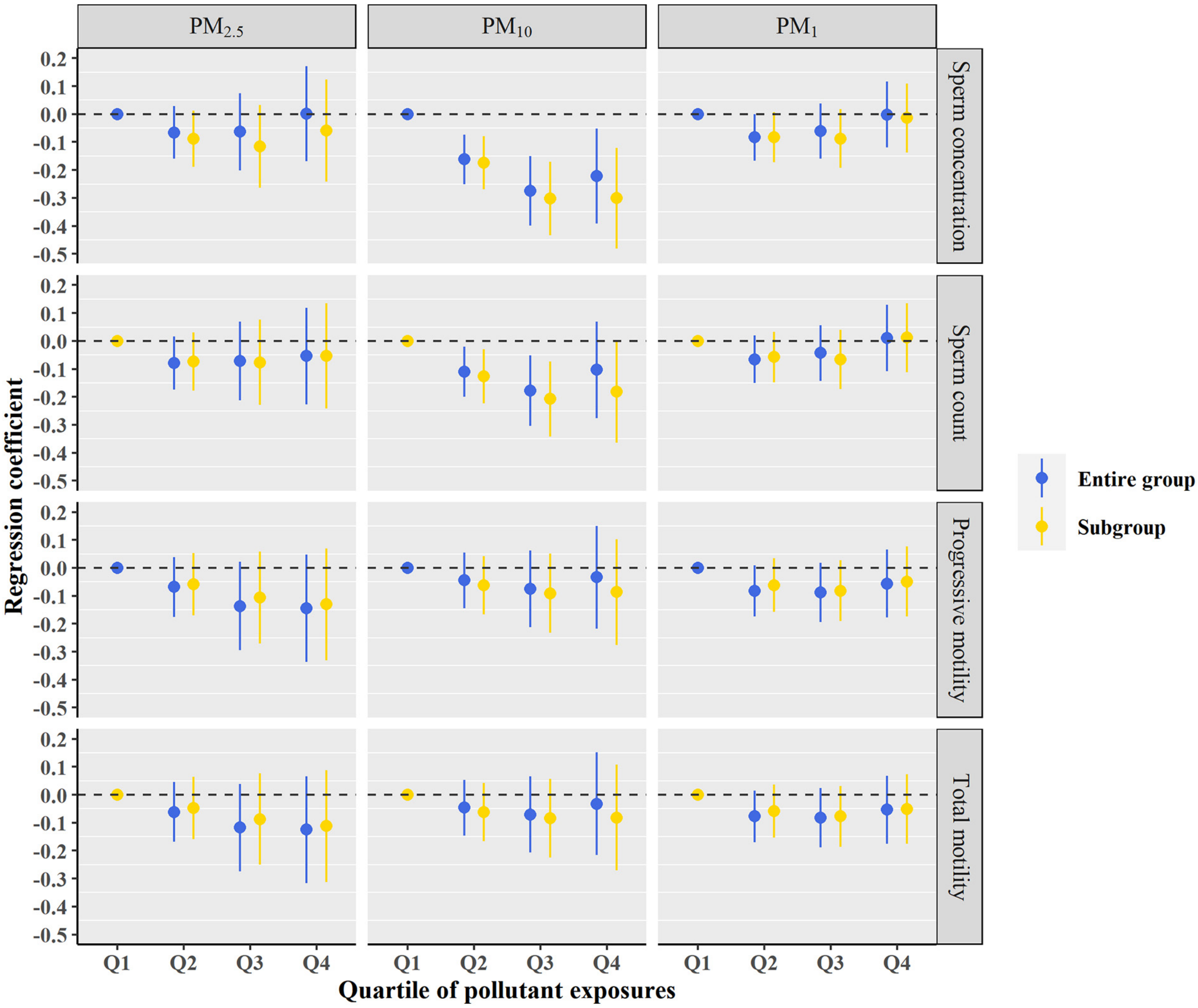

Fig. 6. Regression coefficients and 95 % confidence intervals (CIs) of semen parameters associated with quartiles of pollutant ($PM_{2.5}$, PM_{10}, PM_1) exposures at 0–90 days before the date of semen examination. The models were adjusted for age, BMI, PBF, education, ethnic, marital status, childbearing history, career, smoking, drinking, abstinence period, month and a natural cubic spline function of temperature during exposure period (df = 3). The subgroup only included subjects with normal sperm concentration, sperm count, and motility according to the WHO reference levels for human semen parameters.

sperm motility were found in each separate stratified model, possibly because the relatively small sample sizes are unable to have sufficient power to detect subtle effects (Zhao et al., 2022). These effect modifiers can be taken into account in subsequent analyses.

To the best of our knowledge, this study represents the first attempt to explore the association between PM_1 and semen quality. Previous studies have found the links between PM_1 and all-cause and cardiovascular mortality, emergency hospital visits, and lung cancer (Chen et al., 2017; Guo et al., 2021; Hu et al., 2018; Lin et al., 2016). PM_1 pollution is more detrimental to human health because of its smaller particle size. Existing studies have demonstrated that inhaled fine particles are more likely to be deposited in the pulmonary tract and have a greater contact surface area, thereby promoting systemic inflammation. PM_1 might also carry more toxic and hazardous substances such as metals, which are able to incur greater health effects (Delfino et al., 2005; Valavanidis et al., 2008). We included PM_1 as an interest, but unfortunately, we did not observe the effects of PM_1 on semen quality. Even though relatively reasonable prediction models (R^2 = 0.72) have been reported in our study, the lack of complete ground-monitored PM_1 observations in this paper limits the accurate estimation of the long time series of PM_1 concentrations. Moreover, the health responses to PM pollution are related to various processes and emission sources that form them (Chen et al., 2017). Therefore, PM_1 did not exhibit adverse effects on semen quality homogeneously with $PM_{2.5}$, which may be attributed to the different locations of the PM_1 and $PM_{2.5}$/PM_{10} monitoring stations. Further studies with biological mechanisms linking PM_1 with semen quality are warranted.

Our results have important public health implications. Infertility has become a global public health problem, reportedly affecting 8 to 12 % of reproductive-aged couples worldwide (Fainberg and Kashanian, 2019; Inhorn and Patrizio, 2015). About 20 % - 70 % of infertility may due to male factors (Agarwal et al., 2015). Poor semen quality is considered a major cause of infertility and has been reported to affect reproductive health. Our findings added to the evidence that traffic-related $PM_{2.5}$ and PM_{10} exposure during spermatogenesis may contribute to decreased sperm concentration and sperm count. The decline of sperm concentration in an ejaculation may reduce the probability of getting pregnant because there are fewer sperm available to reach the ovum and fertilize it. Having a lower sperm count also makes it difficult to conceive. Some studies have evaluated the associations between semen parameters and time-to-pregnancy, and their conclusions were not exactly consistent (Buck Louis et al., 2014; Romero Herrera et al., 2021; Zinaman et al., 2000). Considering the downward trend in sperm quality (Wang et al., 2017) and the reported suggestive negative association between PM exposure on it (Deng et al., 2016; Lafuente et al., 2016), there is an urgent need to formulate PM pollution management strategies to reduce the deterioration of semen quality. Meanwhile, we also found that PM pollution diminished semen quality mainly by affecting the late phase of sperm development and that semen quality was potentially modified by obesity and alcohol consumption. This evidence provides helpful scientific information for couples trying to conceive that a healthy lifestyle and enhancement of physical activity could improve the chance of getting pregnant.

There are some strengths in our study. First, we constructed the ensemble tree-based machine learning model to improve the spatio-temporal resolution of air pollutant exposure estimates. RF models comprehensively considered multiple factors highly correlated with traffic-related PM exposure, such as local meteorological factors, traffic indicators, and other geographic information, which not only explain the spatial and temporal variation of traffic-related PM concentration but also can handle non-linear relationships and multicollinearity within variables. High-resolution levels of individual exposure could minimize exposure misclassification and thus provide a more accurate assessment of PM-related effects. Second, our findings indicated that being overweight (PBF ≥ 25 %) and drinking seem to modify the associations between PM exposure and sperm motility. It provided scientific support for the implementation of specific interventions for targeted populations. Third, the commonalities across two-pollutant models and subgroup analyses supported the robustness of our results, suggesting that the relationships between exposures to traffic-related PM and reduced semen quality were stable.

However, some limitations should be noted. First, we evaluated the outdoor ambient air pollution of residential addresses as individual exposures, lacking the indoor environmental quality, and ignored the activity pattern that could have contributed to daily PM exposure concentration. Nevertheless, previous researches have shown a reasonably high correlation between personal and outdoor PM exposure within individuals, and proved that ambient PM concentrations are suitable surrogates for personal PM exposures (Janssen et al., 1998; Massey et al., 2009; Sarnat et al., 2001). Second, even though we adjusted for all available and potential confounders for models, some unmeasured confounding variables such as dietary habits, physical exercise, and drugs may partly influence the associations. Third, other specific semen parameters such as sperm morphology and sperm abnormal head were unable to investigate owing to a lack of data. Fourth, our study may inevitably have selection bias since the sperm donors enrolled from the Human Sperm Bank may be more highly motivated to perform better than people selected at random and could not represent all people. However, some other studies recruited participants from hospitals, those who were infertile men to some extent and may have underlying reproductive problems were more susceptible to air pollution and it will lead to biased estimates (Guan et al., 2020; Zhao et al., 2022). Our study was based on proactive activities of the general population with large sample size, and the selection bias exists but is much smaller. Last, it would be inappropriate to directly extrapolate our findings across populations with a broad spectrum of PM exposure levels.

5. Conclusion

Our study found that exposure to traffic-related $PM_{2.5}$ and PM_{10} pollution throughout spermatogenesis may adversely affect semen quality, especially sperm concentration and count, whereas null associations were found for PM_1. $PM_{2.5}$ and PM_{10} might diminish sperm concentration by mainly affecting the late phase of sperm development. Our findings also implied that overweight and alcohol consumption may modify the relationships between traffic-related PM pollutants and sperm motility. Overall, this study provided more evidence for the negative associations between traffic-related PM exposure and semen quality, highlighting the necessity to reduce ambient air pollution through environmental policy. Further investigation to determine the biological mechanisms underlying the observed associations would be a fruitful direction for future research.

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CRediT authorship contribution statement

Xiaolin Yu: Conceptualization, Data curation, Formal analysis, Methodology, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **Qiling Wang:** Conceptualization, Data curation, Investigation, Project administration, Writing – original draft. **Jing Wei:** Data curation, Visualization. **Qinghui Zeng:** Formal analysis. **Lina Xiao:** Visualization. **Haobo Ni:** Software, Validation. **Ting Xu:** Software, Validation. **Haisheng Wu:** Formal analysis, Methodology. **Pi Guo:** Conceptualization, Supervision, Writing – review & editing. **Xinzong Zhang:** Conceptualization, Data curation, Investigation, Project administration, Supervision, Writing – review & editing.

Data availability

The data that has been used is confidential.

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.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2022.158387.

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