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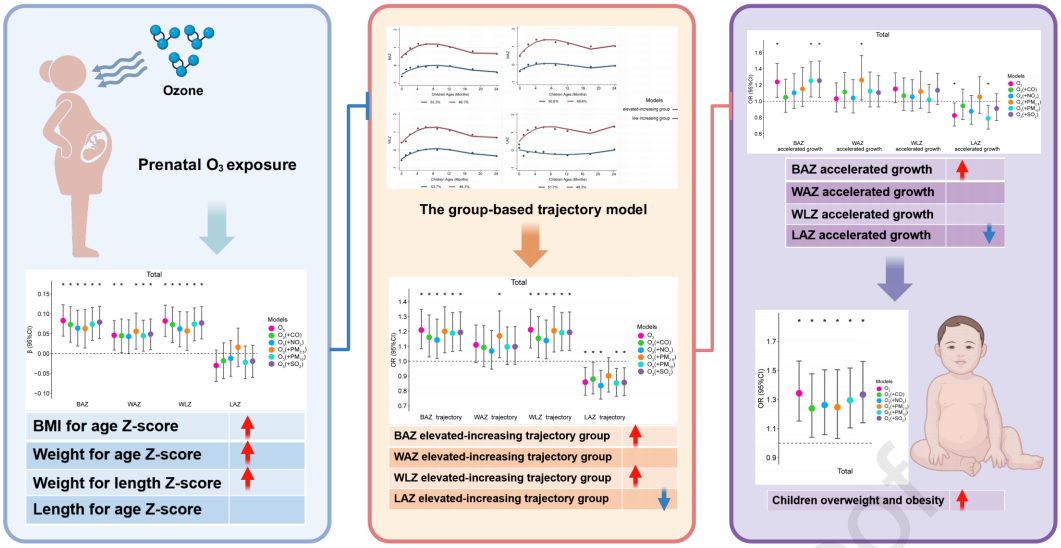

Prenatal ozone exposure is associated with children overweight and obesity: Evidence from the Shanghai Maternal-Child Pairs Cohort

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Abstract:

Prenatal ozone (O_3) exposure may disrupt normal offspring growth. However, epidemiological evidence that prenatal O_3 exposure affects the physical development of offspring early in life is far from adequate. A total of 4,909 maternal–child pairs from the Shanghai Maternal–Child Pairs Cohort (Shanghai MCPC) were included. A high-resolution random forest model was utilized to evaluate prenatal exposure levels of O_3 based on the home addresses of pregnant women. Group-based trajectory and mixed-effects models were used to assess associations between prenatal O_3 exposure and physical parameters. Each 10 μg/m³ increase in O_3 concentration was associated with 0.084, 0.048, and 0.082-unit increases in BMI for age Z score (BAZ), weight for age Z score (WAZ), and weight for length Z score (WLZ), respectively. Specifically, a 10 μg/m³ increase in O_3 concentration was linked to a 1.208-fold and 1.209-fold increase in the elevated-increasing group for the BAZ and WLZ trajectories, respectively. Moreover, each 10 μg/m³ increase in prenatal O_3 was associated with a 1.396-fold and 0.786-fold increase in the risk of BAZ- and length for age Z score (LAZ)-accelerated growth, respectively. Furthermore, a 10 μg/m³ increase in prenatal O_3 was linked to a 1.355-fold increase in the risk of overweight and obesity (OAO). Our study revealed that prenatal O_3 exposure is associated with accelerated BMI gain or decelerated body length gain in the early life of children. Prenatal O_3 may also increase the risk of OAO in children for the first two years.

Keywords: Ozone; Accelerated growth; Obesity and overweight; Child growth trajectories; Birth cohort

1. Introduction

Overweight and obesity (OAO) have become global public health concerns that pose a significant burden on both developed and developing nations[1]. From 1999 to 2016, there was a significant increase in the incidence of obesity in both adolescents and adults[2]. The prevalence of childhood obesity is increasing worldwide, with 158 million children aged 5 to 19 years suffering from obesity in 2019[3]. Body mass index (BMI) standard deviation scores for OAO adolescents aged 15–18 years were already elevated during infancy and continued to increase throughout childhood, contrasting with those of individuals with normal or lighter weights[4]. The onset of obesity rebounding between the ages of 3.5 and 5 is linked to elevated BMI and an overall increased risk of obesity during adolescence[5]. Rapid child growth has been shown to be associated with a higher risk of obesity, cardiovascular disease, or several metabolic diseases later in life[6-9]. A recent meta-analysis revealed that rapid weight gain during the first two years of life was significantly linked to a 3.66-fold increased likelihood of developing OAO, as well as an elevated risk of various health conditions in adulthood, including hypertension, obesity, cardiovascular disease, diabetes, and metabolic syndrome[10-12].

In addition to the predetermined genetic effects, children's growth trajectories are vulnerable to modifiable factors, including socioeconomic, behavioral, and environmental factors[13]. As a modifiable environmental factor, air pollution has received increasing amounts of attention. Recent studies have shown that prolonged air pollution exposure can result in weight gain and an elevated risk of developing metabolic syndrome and obesity [14-16]. However, a systematic review revealed conflicting conclusions regarding the correlation between air pollution and obesity. Among the studies reviewed, 44% identified a positive correlation, 12% indicated a negative correlation, and 44% found no significant correlation[17]. Following the release of the new air quality guideline (AQG) in 2021, PM has been effectively controlled, and ozone (O_3) is considered the predominant pollutant in ambient air worldwide. O_3 is a major air pollutant and the primary constituent of photochemical smog[18]. Due to continued global climate change and anthropogenic emissions, most parts of China have shown a rapid upward trend in air pollution, especially in the eastern region and southeastern coastal areas[19]. Previous studies based on field observations and satellite retrievals have highlighted severe O_3 pollution in China. The hourly maximum O_3 concentrations recorded in China frequently exceeded 321.45 $\mu g/m^3$[20, 21].

The initial twenty-four months of life play an essential role in individual development and lay the foundation for programming long-term health outcomes[22]. Pregnant women and children are uniquely vulnerable to air pollution, and prenatal exposure to air pollution may have lasting effects on the physical development of offspring[23]. Several recent epidemiological studies have explored the connection between O_3 exposure and OAO in children. Dong et al. reported that exposure to elevated concentrations of O_3 was associated with a greater risk of OAO in children aged 2–14 years[24]. A study of 9- to 17-year-old children revealed that for every 10 $\mu g/m^3$ increase in O_3 exposure, there was a corresponding 4.1% increase in the risk of obesity in Jiangsu Province, China[25]. Two prospective studies demonstrated that prenatal O_3 exposure is positively associated with increased postnatal fat mass and body fat percentage, with 1–6 month weight gain [26, 27]. In mouse models, prenatal O_3 exposure was proven to disturb energy imbalances and dyslipidemia, and ultimately induce an OAO phenotype in offspring[28]. These studies, however, were limited to individual aspects of growth or specific time points. Longitudinal evidence regarding the effect of prenatal O_3 exposure on children's physical growth, development, and obesity is relatively limited. As children's body mass index may fluctuate over time, evaluating the association between prenatal O_3 exposure and OAO solely through singular time-point body mass indices might be insufficient[29]. Childhood growth trajectories significantly impact morbidity and mortality across the lifespan, potentially influenced by environmental factors[30]. Future studies should aim to track the trajectory patterns of child growth throughout childhood development. These studies, examining children's growth patterns over time, are crucial for comprehensively elucidating the relationship between prenatal O_3 exposure and childhood physical development. These findings hold promise for offering insights into the impacts of such exposure on diverse growth trajectories.

Therefore, based on the Shanghai Maternal–Child Pairs Cohort (Shanghai MCPC), a high-resolution random forest algorithm model was applied to estimate prenatal O_3 exposure during a spatial 1 km resolution in this study. The growth parameters of the multitemporal children were measured, as was the trajectory model. We investigated the associations between prenatal O_3 concentrations and children's growth in terms of their physical parameters, growth trajectories, accelerated growth, and OAO.

2. Methods

2.1. Study participants

The participants in the study were maternal–child pairs from the Shanghai MCPC[31]. The inclusion and exclusion criteria and protocols were as follows: 1) lived in Shanghai for more than a year prior to becoming pregnant; 2) were at least 20 years of age and did not experience any communication barriers; and 3) were pregnant for 12–16 weeks, with follow-up prenatal examination and delivery planned to be carried out in the two hospitals allocated by the project; 4) had no history of serious chronic diseases or infectious diseases such as hypertension, diabetes, heart disease, or mental illness; 5) signed the informed consent form and were willing to complete the questionnaire survey and follow-up survey after birth.

Between April 2016 and October 2018, a total of 6,782 maternal–child pairs were recruited for this research. After excluding 229 patients, we further excluded 914 pregnancies with complications (gestational hypertension, eclampsia, and gestational diabetes mellitus) and pregnancies that ended in abortion, as well as 77 twin pregnancies, leaving 5,562 children for follow-up. All participants were invited to complete physical development examinations at approximately 1, 2, 4, 6, 9, 12, 18, and 24 months. In total, 4,909 mother–child pairs completed all the physical examinations. A detailed flow chart of the process is shown in Figure S1. The research protocol received approval from the ethics committee of Fudan University (IRB#2016-04-0587-EX), and written informed consent was obtained from all participants or their authorized representatives.

2.2. Assessment of air pollutant exposure

A daily maximum of 8 hours of O_3 exposure during pregnancy was estimated using a 1 km × 1 km resolution and predicted through a full temporospatial coverage model developed by Meng et al.[32]. Detailed information on the model has been published previously. The model integrates ground-level O_3 measurements, O_3 simulations from the community multiscale air quality (CMAQ) modeling system, meteorological parameters, population density, road length, and altitude to forecast O_3 concentrations. Validation of the model indicated a daily level cross-validation R^2 of 0.80, with mean absolute percentage error (MAPE) and root mean square error (RMSE) values of 29.60% and 20.93 μg/m^3, respectively. The random forest model, developed by Meng et al., was utilized to predict the daily average $PM_{2.5}$ exposure concentration at a resolution of 1 km × 1 km. This model achieved an R^2 of 0.81 and an RMSE of 18.5 μg/m^3 for the full-coverage predictions at the daily level[33, 34]. Furthermore, daily estimates of traditional air pollutants (CO, NO_2, PM_{10},

and SO_2)were derived from fixed monitoring stations located in Shanghai. The average individual concentrations of air pollutants during the whole pregnancy were calculated.

2.3 Physical examination of children's growth

Birth length, birth weight, and other data were acquired from obstetric records. Physical growth and development measurements, examinations, and feeding data were recorded and collected by trained child health doctors when the children reached the ages of 1, 2, 4, 6, 9, 12, 18, or 24 months. To measure the body length of babies, they were asked to remove their shoes, hats, and socks; lie flat on the measuring board on their back; keep their legs straight; put their heads straight; touch the top plate with their heads; and ensure that their ears were at the same level, with an accuracy of 0.1 cm. Body weight was recorded simultaneously with a precision of 0.01 kg. Standardization of physical growth and developmental metrics was performed for the children. The R package "anthro" (version number: 1.0.0.9000) was used to convert the Z scores of the physical parameters. Based on the World Health Organization's 2006 standards for growth and development for children, the BMI for age Z score (BAZ), weight for age Z score (WAZ), weight for length Z score (WLZ), and length for age Z score (LAZ) were acquired. Subsequently, the researchers calculated the difference between the Z score at different months and at birth. Accelerated growth is a phenomenon in which the body grows at a rate that exceeds the general level of development for the same age, and accelerated growth often occurs in early childhood[35]. Z score of 0.67 represents the width of each percentile range on the standard growth curve chart, ranging from the second percentile to the ninth percentile, the ninth percentile to the 25th percentile, the 25th percentile to the 50th percentile, and so forth[36]. We characterized accelerated growth as the instance when the difference between the Z score at each month of age and at birth equaled or exceeded 0.67[35, 36]. Conversely, growth below this threshold was categorized as non-accelerated. OAO was classified according to the BAZ value, with a BAZ value > P_{85} indicating OAO[37].

2.4 Covariates

The following data were collected during pregnancy: age at delivery; annual household income (< 100k CNY/year, 100–300k CNY/year, and > 300k CNY/year); maternal education level (junior high school and below, senior secondary, postsecondary, or university and above); gestational weight gain (GWG); maternal and paternal height; and passive smoking during pregnancy. The physical activity levels (mild, moderate, and severe) of the pregnant women during the early stages

of pregnancy were evaluated utilizing the Short Form of the International Physical Activity Questionnaire (IPAQ). Preconception BMI was assessed by measuring maternal height with a stadiometer and recording self-reported weight before conception. Additional significant covariates were gathered from medical records at the hospital, including parity (primipara, multipara), child gender (male, female), premature birth (yes or no), breastfeeding duration, gestational weeks at delivery, birth weight, birth length and follow-up time. Daily estimates of relative humidity and temperature were derived from fixed monitoring stations in Shanghai.

2.5. Statistical analysis

The primary characteristics of the subjects were described and reported using descriptive statistics. For normally distributed continuous variables, the mean value ± standard deviation (mean ± SD) was used to present the results, while the frequency and composition ratio (%) were used to express categorical variables. Independent sample t tests were used to evaluate the growth parameter characteristics of the children. Pearson correlation was used to assess the correlation between O_3, CO, $PM_{2.5}$, PM_{10}, NO_2, and SO_2 in the whole pregnancy.

Mixed-effects models are well suited for handling repeated-measures data, integrating both fixed and random effects to reveal individual disparities and variability inherent in longitudinal datasets. In our study, linear mixed-effects models were employed to investigate the longitudinal association between prenatal O_3 exposure and child growth parameters.

Multivariate regression analysis (MLR) is a widely employed statistical technique for assessing multifaceted relationships between multiple independent variables and a dependent variable in a linear context. In our study, the MLR was employed to evaluate the cross-sectional association between prenatal O_3 exposure and growth parameters across children of various ages. The estimated coefficients (β) obtained from these models were interpreted as the change in child growth parameters associated with each 10 $\mu g/m^3$ increase in prenatal O_3 exposure. The group-based trajectory model (GBTM) is a human-centered, semiparametric methodology widely applied in longitudinal studies; it operates on the premise that distinct groups within the study population possess unique developmental pathways. This approach focuses on delineating shifts in developmental patterns, behaviors, or health/disease status over time. The GBTM facilitates the exploration of specific outcome trajectories and the identification of groups or categories sharing similar patterns, thereby revealing diverse developmental pathways[38-40]. In this study, the GBTM

was used to scrutinize children's developmental trajectories throughout their initial two years of life. Central to GBTM analysis is the selection of an apt model. Initially, we modeled 1 to 5 trajectory groups, leveraging the Bayesian information criterion (BIC) to discern the optimal number of groups, favoring the model with the highest absolute BIC value. We further identified trajectory shapes that accurately mirrored the observed patterns by evaluating linear, quadratic, and cubic functions. The model demonstrating the highest fit was chosen based on the BIC value, ensuring an average a posteriori probability (AvePP) of ≥ 0.70 for each trajectory and a representation of at least 5% of the total sample size for each trajectory[39, 41]. The GBTM fits for specific parameters are detailed in Table S1, incorporating children with data available from at least three follow-up visits (n = 4,909). After determining the optimal number of clusters per trajectory, we displayed the respective paths for every measurement through graphical representation. Additionally, we acquired the child growth trajectory groups, the new outcome variables, through the employment of the GBTM model. This group was best represented by the BAZ, WAZ, WLZ, and LAZ and divided into two categories (low-increasing group and elevated-increasing group). The low-increasing group was determined to be the reference category.

In addition, generalized mixed-effects models were employed to explore the association between prenatal O_3 exposure and child growth acceleration and OAO, taking into account the repeated-measures data obtained from individual subjects. Furthermore, logistic regression models were used to evaluate the associations between prenatal O_3 exposure and various factors, such as child growth trajectory groups, accelerated growth, and OAO, at various months of age. The estimated odds ratios (ORs) and 95% confidence intervals (CIs) derived from these models were interpreted as the risk linked to every 10 $\mu g/m^3$ increase in O_3 exposure. Upon adjusting the *P* values for multiple testing utilizing the false discovery rate (FDR), a significance threshold of less than 0.1 was adopted for evaluating the correlation of constituents with child growth measures[42, 43]. Finally, to investigate the potentially confounding effects of common pollutants, two-pollutant models were constructed to test the robustness of the single-pollutant model developed in this study. To perform sensitivity analyses, we eliminated pregnant women who gave birth prior to the 37th week of pregnancy. Gender-stratified analysis and the interaction between prenatal O_3 exposure and gender were performed at the same time. In our analyses, we included the following covariates: prepregnancy BMI, age at delivery, annual household income, maternal education level,

breastfeeding duration, maternal height, paternal height, GWG, passive smoking during pregnancy, birth length, birth weight, IPAQ, age of children at follow-up (months), preterm birth, gestational weeks at delivery and parity. All analyses were accomplished using Stata (version 17) and R software (version 4.1.2). All the statistical tests were two-sided, and the significance level was set at $\alpha = 0.05$.

3. Results

3.1. Participant characteristics and child growth parameters

Table 1 presents the characteristics of the maternal–child pairs (n = 4,909). The average age at delivery was 28.7 ± 4.14 years, with a mean prepregnancy BMI of 21.2 ± 2.91 kg/m^2. The proportion of pregnant women with a college degree or higher in the total group of pregnant women was 42.5%. Additionally, 56.8% of the pregnant women were primiparous. The children born included 51.6% boys and 48.4% girls, with 4.16% being preterm births. The average birth length and birth weight were recorded as 50.0 ± 0.93 cm and 3,333 ± 436 g, respectively. At 4, 6, and 9 months of age, significant gender-specific differences were observed in the BAZ, WAZ, WLZ, and LAZ, as well as in body weight, body length, and BMI (Table S2 and Table S2). The growth curve for childhood is shown in Figures S3 and S4.

Table 1 Participant characteristics (n = 4,909)

Participants characteristic	Mean ± SD / n(%)
Age at delivery, years	28.7 ± 4.14
Maternal height	161 ± 4.78
Paternal height	174 ± 5.16
Prepregnancy BMI, kg/m^2	21.2 ± 2.91
Gestation weight gain (GWG), kg	14.4 ± 5.29
Maternal education levels	
Junior high school or below	552 (11.2%)
Senior secondary	659 (13.4%)
Postsecondary	1,611 (32.8%)
College degree or higher	2,087 (42.5%)
Annual household income, CNY/year	
≤ 100k	1,274 (26.0%)

100–300k	3,195 (65.1%)
> 300k	440 (8.96%)
Passive smoking during pregnancy	
Yes	743 (15.1%)
No	4,166 (84.9%)
Physical activity during pregnancy	
Mild	1,918 (39.1%)
Moderate	2,749 (56.0%)
Severe	242 (4.93%)
Parity	
Primipara	2,786 (56.8%)
Multipara	2,123 (43.2%)
Child gender	
Boy	2,533 (51.6%)
Girl	2,376 (48.4%)
Birth weight, g	3,333 ± 436
Birth length, cm	50.0 ± 0.93
Premature birth	
Yes	204 (4.16%)
No	4,705 (95.8%)
Gestational weeks at delivery	39.3 ±1.45
Duration of breastfeeding (month)	9.26 ± 4.47

Preterm birth, gestational age < 37 weeks; passive smoking during pregnancy, the average weekly > 1 time, each time more than 15 min.

3.2. Concentration distributions of O_3 exposure

Table 2 presents the concentrations of O_3 exposure and meteorological characteristics during the whole pregnancy for all pregnant women. The median concentrations of O_3, CO, NO_2, $PM_{2.5}$, PM_{10} and SO_2 during pregnancy were 94.00 μg/m^3, 0.73 mg/m^3, 36.24 μg/m^3, 38.39 μg/m^3, 51.44 μg/m^3 and 9.52 μg/m^3, respectively. O_3 exhibited a negative correlation with other pollutants (CO, NO_2, $PM_{2.5}$, and PM_{10}), except for SO_2, which ranged from -0.47 to -0.02 (Figure S2).

Table 2 O_3 exposure and meteorological characteristics of pregnant women during pregnancy

Exposure	**Mean**	**SD**	**Min**	***P*$_{25}$**	**Median**	***P*$_{75}$**	**Max**	***IQR***

characteristics								
O_3, μg/m^3	95.34	8.51	76.86	88.24	94.00	102.07	118.55	13.83
CO, mg/m^3	0.74	0.07	0.54	0.70	0.73	0.79	1.01	0.08
NO_2, μg/m^3	36.83	5.96	22.00	32.70	36.24	41.95	51.12	9.25
$PM_{2.5}$, μg/m^3	37.83	4.02	25.60	35.04	38.39	40.57	56.11	5.53
PM_{10}, μg/m^3	50.53	6.91	35.38	44.37	51.44	55.37	77.88	11.00
SO_2, μg/m^3	9.20	1.93	4.49	7.63	9.52	10.34	18.07	2.70
Temperature, ℃	18.61	2.59	10.66	16.12	19.06	21.00	25.32	4.88
Humidity, %	73.47	3.03	67.06	70.44	74.14	75.33	80.88	4.89

Min, the minimum value; P_{25}, the 25th percentile; P_{75}, the 75th percentile; Max, the maximum; *IQR*, the inter-quartile range.

3.3. Associations between prenatal O_3 exposure and child growth parameters

Associations of prenatal O_3 exposure with the BAZ, WAZ, WLZ, and LAZ are shown in Figures 1 and S5. The relationships between O_3 and child growth in both the single- and two-pollutant models, as identified through linear mixed-effect models, are depicted in Figure 1. Within the total population, the effect estimates for 10 μg/m^3 O_3 were 0.083 (95% CI: 0.044 to 0.123), 0.046 (0.009 to 0.083), and 0.082 (0.043 to 0.122) unit increases in the BAZ, WAZ, and WLZ, respectively. The associations remained significant for BAZ, WAZ, and WLZ in the two-pollutant models after we adjusted for CO, NO_2, $PM_{2.5}$, PM_{10}, and SO_2.

Figure 1. Associations between prenatal O_3 exposure (each 10 μg/m^3) and child growth parameters (β, 95% CIs) using linear mixed-effects model. Models were adjusted for prepregnancy BMI, age at delivery, annual household income, maternal education levels, breastfeeding duration, maternal height, paternal height, GWG, passive smoking during pregnancy, birth length, birth weight, IPAQ, age of children at follow-up (months), preterm birth, gestational weeks at delivery, and parity.

The associations between prenatal O_3 exposure and child growth parameters, as analyzed by the MLR, are presented in Figure S5. For total population, prenatal O_3 (each 10μg/m^3) was positively related to BAZ and WLZ at 1, 2, 4, 6 and 18 months of age, and to WAZ at 2, 4, 6 and 18 months of age[$\beta_{BAZ\text{-}1m}$: 0.091 (0.032, 0.151); $\beta_{BAZ\text{-}2m}$: 0.106 (0.052, 0.160); $\beta_{BAZ\text{-}4m}$: 0.176 (0.116, 0.236); $\beta_{BAZ\text{-}6m}$: 0.126 (0.068, 0.185); $\beta_{BAZ\text{-}18m}$: 0.176 (0.115, 0.236); $\beta_{WAZ\text{-}2m}$: 0.058 (0.009, 0.107); $\beta_{WAZ\text{-}4m}$: 0.081 (0.026, 0.137); $\beta_{WAZ\text{-}6m}$: 0.076 (0.022, 0.130); $\beta_{WAZ\text{-}18m}$: 0.130 (0.071, 0.189); $\beta_{WLZ\text{-}}$

$_{1m}$: 0.107 (0.040, 0.173); β_{WLZ-2m}: 0.120 (0.063, 0.177); β_{WLZ-4m}: 0.178 (0.118, 0.238); β_{WLZ-6m}: 0.124 (0.067, 0.182); $\beta_{WLZ-18m}$: 0.172 (0.113, 0.231)]. The longitudinal analysis in Figure 1 supports these consistent findings. Additionally, increased prenatal O_3 levels (at 10 μg/m^3) can lead to a reduction in the LAZ at four months of age [β_{LAZ-4m}: -0.088 (-0.144, -0.031)].

3.4. Associations between prenatal O_3 exposure and children's growth trajectories

In this study, the GBTM distinguished two trajectory groups for child growth parameters (BAZ, WAZ, WLZ, and LAZ). Figure S6 illustrates the trajectories for each measurement. There were two trajectory groups for each parameter related to children's growth: low-increasing and elevated-increasing. For all the measurements, the low-increasing group was chosen as the reference group. Comprehensive definitions of the trajectory groups and model selection criteria (including AvePP and BIC) are shown in Table S1. The correlation between prenatal O_3 exposure and children's growth trajectories is shown in Figure 2. Each 10 μg/m^3 increase in prenatal O_3 resulted in a 1.210-fold and 1.212-fold increase in the risk of elevated BAZ and WLZ, respectively. The risk of prenatal O_3 in the LAZ elevated-increasing group decreased with a 10 μg/m^3 increase in prenatal O_3, with an OR of 0.859-fold. The associations between BAZ and WLZ remained significant after we adjusted for CO, NO_2, $PM_{2.5}$, PM_{10}, and SO_2 in the two-pollutant models. In addition, prenatal O_3 exposure had no effect on WAZ trajectories, but this effect was enhanced by co-adjustment with SO_2. However, co-adjustment for $PM_{2.5}$ attenuated the impact of prenatal O_3 exposure on the LAZ.

Figure 2. Associations between prenatal O_3 exposure (each 10 μg/m^3) and children's growth trajectories using logistic regression models. *: $P < 0.05$. Models were adjusted for prepregnancy BMI, age at delivery, annual household income, maternal education levels, breastfeeding duration, maternal height, paternal height, GWG, passive smoking during pregnancy, birth length, birth weight, IPAQ, age of children at follow-up (months), preterm birth, gestational weeks at delivery, and parity.

3.5. Associations between prenatal O_3 exposure and accelerated growth in children

BAZ, WAZ, WLZ, and LAZ were classified as accelerated or non-accelerated growth based on the difference in Z scores at each month of age and at birth. Figure 3 illustrates the association between O_3 exposure and accelerated growth (generalized mixed effect model). For the total population, an increase of 10 μg/m^3 in O_3 concentration was linked to a 1.239-fold increase in

accelerated growth risk associated with BAZ. The risk of accelerated LAZ growth was found to decrease with each 10 μg/m^3 increase in O_3, with an OR of 0.826-fold. Moreover, no association between prenatal O_3 and accelerated growth in the WAZ or WLZ was found in this study. Additionally, no gender differences were found for BAZ, WAZ, or WLZ; however, LAZ had an OR of 0.763, and girls were more susceptible than boys. Logistic regression models were used to assess the associations between prenatal O_3 exposure and accelerated growth in children at various months of age (Figure S7), and the findings aligned with the findings from the longitudinal analysis presented in Figure 3. For total and female children, the prenatal O_3 concentration was associated with an increased risk of accelerated growth in WLZ children at 4 and 18 months, respectively, and accelerated growth in BAZ children at 4 months, with an OR ranging from 1.195 to 1.247.

Figure 3. Associations between prenatal O_3 exposure (each 10 μg/m^3) and accelerated growth in children using generalized mixed-effects models. *: $P < 0.05$. Models were adjusted for prepregnancy BMI, age at delivery, annual household income, maternal education levels, breastfeeding duration, maternal height, paternal height, GWG, passive smoking during pregnancy, birth length, birth weight, IPAQ, age of children at follow-up (months), preterm birth, gestational weeks at delivery, and parity.

3.6. Effects of prenatal O_3 exposure on OAO in children

The associations between O_3 exposure and OAO, as ascertained by generalized mixed-effects models, are visualized in Figure 4. An increase of 10 μg/m^3 in prenatal O_3 concentration was associated with 1.343, 1.293, and 1.293-fold increases in the total risk of OAO for male and female children, respectively. The trend in the two pollutants remained consistent. No gender specificity was found for OAO in these children. Logistic regression models were used to evaluate the correlations between O_3 exposure and children's OAO at different months of age (Figure S8), and the findings obtained were consistent with the longitudinal analysis results presented in Figure 4. In the total population, prenatal O_3 exposure was associated with an elevated risk of OAO in children at 2, 4, 6, and 18 months of age, with ORs ranging from 1.196 to 1.507.

Figure 4. Associations between prenatal O_3 exposure (each 10 μg/m^3) and OAO in children (OR, 95%CIs) using generalized mixed-effects models. *: $P < 0.05$.

3.7. Sensitivity analysis

The positive effects of prenatal O_3 exposure and childhood OAO were robust after excluding preterm birth (Figure S9). After adjusting for CO, NO_2, PM_{10}, and SO_2, the associations of O_3 with OAO in children remained significant according to the two-pollutant models. No interaction between prenatal O_3 exposure and gender was found, as shown in Tables S4-S7.

4. Discussion

In this study, we found that prenatal O_3 exposure could accelerate early childhood growth and increase the risk of OAO, especially at 4, 6, and 18 months after birth. The exposure concentrations of O_3 were higher than those in other cities in China and the United States[44-46]. Variations in the methods used for assessing O_3 exposure and geographic location might account for the higher O_3 exposure levels observed in this study than in previous reports. Herein, to avoid misclassification bias, O_3 exposure was simulated using a high-resolution model that considered spatial and temporal parameters, as well as individuals with near-surface meteorological conditions. As a result, individual levels of O_3 exposure are more precise than exposure estimates obtained from fixed monitoring stations[32].

Early life weight gain is an indicator of obesity and related metabolic disorders among adults. Our findings indicate that prenatal O_3 exposure is positively associated with BAZ, WAZ, and WLZ in children and may increase the risk of accelerated growth and OAO. Our findings were consistent with previous results. During a follow-up study of 5-month-old children, it was determined that O_3 exposure during late gestation resulted in a considerable increase in body fat percentage of 2.2% per interquartile range and 2.1% per 100 days, as well as a daily fat mass increase of 1.8 grams throughout the time frame from birth to 5 months[26]. In children aged 9 to 17 years, each increase of 10 $\mu g/m^3$ in O_3, $PM_{2.5}$, or NO_2 was connected with a heightened risk of obesity, with associated ORs of 1.041, 1.185, and 1.127, respectively[25]. Su et al. reported that air pollution can promote the development of OAO in preschool children[47]. One possible explanation for this finding is that O_3 exposure might augment the risk of accelerated growth, potentially leading to the occurrence of OAO in children.

In addition, we further explored the effect of prenatal O_3 on children's growth trajectories. Our results showed that higher prenatal O_3 concentrations were associated with greater odds of BAZ and WLZ elevated-increasing groups and LAZ low-increasing groups in children. Traditional studies

use cross-sectional methods that fail to capture the inherent variability and dynamics of growth patterns. Much of the previous literature has relied primarily on fixed growth metrics, ignoring children's dynamic growth patterns. The GBTM can provide a dynamic perspective from which to explore children's growth patterns. The effects of differences in growth trajectories early in life may persist through childhood, adolescence, and adulthood.

Research on the association between prenatal O_3 concentrations and children's growth trajectories is still limited. Only a few relevant studies have explored the relationships between other pollutants and children's growth trajectories. For instance, a large longitudinal study showed that exposure to NO_2, PM_{10}, and $PM_{2.5}$ was associated with a small increase in BMI from birth to 5 years of age in children[48]. Another study explored the relationship between prenatal phthalate exposure and the body roundness index and body shape index trajectory groups in childhood. In brief, prenatal exposure to phthalates increases the risk of childhood obesity, which is primarily related to inflammatory responses and the regulation of lipid metabolism[49]. In our study, no effect of prenatal O_3 exposure on the LAZ was found. However, prenatal O_3 reduced the risk of elevated-increasing groups and accelerated growth in the LAZ. These findings were similar to those of a study conducted in Ghana, where researchers reported that prenatal CO exposure decreased LAZ while increasing risk in the lower LAZ group[30]. Gender dimorphism in OAO was also found in these children, with prenatal O_3 exposure increasing the risk of OAO in girls at 2 and 6 months of age compared to that in boys. The longer window of sensitivity in girls than in boys may be attributed to the fact that females are more susceptible to O_3 exposure than males [50]. The results of previous animal studies have shown differences in placental metabolic programmes between boys and girls, which may also contribute to the different effects of prenatal O_3 exposure on the growth of boys and girls[51, 52].

The mechanisms by which prenatal O_3 exposure contributes to childhood obesity are unclear, but recent studies have shown that these mechanisms may be related to placental epigenetic regulation, lipid metabolism, inflammation, or oxidative stress. There is increasing evidence supporting the hypothesis that air pollution exposure contributes to obesity by disrupting lipid metabolism. A study revealed increased blood lipid levels and adipose tissue accumulation in individuals exposed to high air pollution levels[53]. Recent research has suggested that increased exposure to O_3 is linked to an increase in fat mass but is negatively correlated with lean muscle

mass[54]. Multiple studies have shown that exposure to O_3 can increase the levels of both total cholesterol and triglycerides, which can lead to an increased risk of dyslipidemia[15, 55-57]. Even low levels of O_3 can induce lipid accumulation in human adult stem cells derived from adipose tissue[53]. Research has revealed that exposure to O_3 significantly increases human serum corticosterone and cortisol levels, while also elevating the levels of medium and long-chain free fatty acids, glycerol, and monoglycerides[58]. An animal experiment demonstrated that acute O_3 exposure can rapidly activate the hypothalamic-pituitary-adrenal axis, leading to an increase in corticosterone levels[59]. Substantial evidence suggests that alterations in the in utero environment during early developmental stages may impact epigenetic inheritance, subsequently causing permanent changes in neonatal metabolic processes[60]. The above studies showed that exposure to air pollution can seriously affect the development of adipose tissue and its metabolic function, thus affecting the risk of developing obesity. Moreover, studies on animals have shown that O_3 exposure causes oxidative stress and adipose inflammation, which are both contributing factors to obesity[61]. Another animal study revealed that O_3 exposure in rats interfered with placental mitochondrial function, possibly affecting fetus energy supply and development[52, 62]. The placenta serves as the sole conduit for delivering nutrients to the fetus during pregnancy; hence, the health and functionality of the placenta are intimately linked to the healthy development of the fetus[63]. However, due to its heightened metabolic activity and extensive cellular turnover, the placenta is exceedingly sensitive to oxidative stress[64]. Within the placenta, oxidative stress-induced DNA damage, lipid peroxidation, and protein denaturation can alter placental function, diminishing the capacity of the placenta to convey oxygen and nutrients to the fetus[65]. Mitochondria serve as both the primary site for generating reactive oxygen species and the focal point of their attack, potentially inducing alterations in their functionality[66, 67]. Reports have highlighted a strong correlation between oxidative stress and impaired placental mitochondrial function in expectant mothers[68]. Research indicates that compromised mitochondrial function in the placenta could impact both placental health and the subsequent growth of the fetus[66, 68]. Moreover, research has shown that DNA methylation in the placenta and umbilical cord blood serves as a biological target for prenatal exposure to O_3[69]. DNA methylation markers may lead to dysregulation of TFAP2E and FAM3C expression in placental tissues and are associated with early childhood adiposity[70]. This provides some mechanistic evidence that prenatal O_3 exposure

contributes to childhood OAO.

This study has several strengths. We conducted the present study based on a prospective cohort study design, which enhances the body of scientific evidence supporting the positive associations between prenatal O_3 exposure and OAO risk in children. Furthermore, a high-resolution O_3 assessment model was used to assess individual prenatal O_3 exposure instead of relying on fixed monitoring stations. This approach improves the accuracy of exposure assessment and minimizes exposure misclassification bias[32]. Moreover, by utilizing the GBTM, this study modeled children's growth trajectories and assessed the association between prenatal O_3 exposure and these trajectories. While conventional techniques use a cross-sectional framework that neglects the dynamic aspects and innate variances of growth patterns, GBTM offers a dynamic perspective on patterns of child growth, and deviations in early-life growth trajectories may have long-lasting effects on children.

Nonetheless, there were several limitations to this study. First, we estimated only outdoor O_3 concentrations based on residences, neglecting indoor pollution concentrations or other micro-environments that may contribute to O_3 exposure. Second, although we considered the primary confounding factors linked to O_3 exposure and the risk of OAO in our analysis, our findings may still be impacted by other factors, such as co-pollutants. Two-pollutant models were utilized to assess the robustness of the results, which could partially adjust for the effect of co-pollutants exposure. O_3 exposure levels were determined based on the residency address of the participants. However, the presence of pregnant women at their workplace, albeit for a certain duration, could give rise to specific limitations. Future research could consider a more comprehensive assessment of participants' activity locations to better understand the health effects of O_3 during pregnancy.

5. Conclusion

In summary, our study provided unique insights into prenatal O_3 exposure and its effects on children's growth trajectories. These findings showed that prenatal O_3 exposure is associated with accelerated BMI gain or decelerated body length gain and may ultimately increase the risk of OAO in the early life of children. To further improve the health of future generations, prenatal care guidelines and public policies should be implemented to avoid high levels of O_3 exposure during pregnancy. Furthermore, additional research is needed to confirm our findings and to elucidate the biological mechanisms underlying the observed relationships.

Ethics approval and consent to participate

The research protocol was approved by the ethics committee of Fudan University (IRB#2016-04-0587-EX), and all participants or their respondents provided written informed consent.

CRediT authorship contribution statement

X.Y.S.: conceptualization, formal analysis, visualization, methodology, software, writing–original draft, writing–review & editing; L.Y.Z.: investigation, methodology, writing–review & editing; W.Q.X.: methodology, resources; X.M.: investigation, methodology; Y.Z., Y.Y.G.: methodology; H.J.S.: supervision, resources; P.P.W.: methodology, writing–review & editing, resources, supervision; Y.H.Z.: conceptualization, resources, validation, writing–review & editing, supervision, project administration, funding acquisition.

Declaration of competing interests

The authors declare no competing financial interests.

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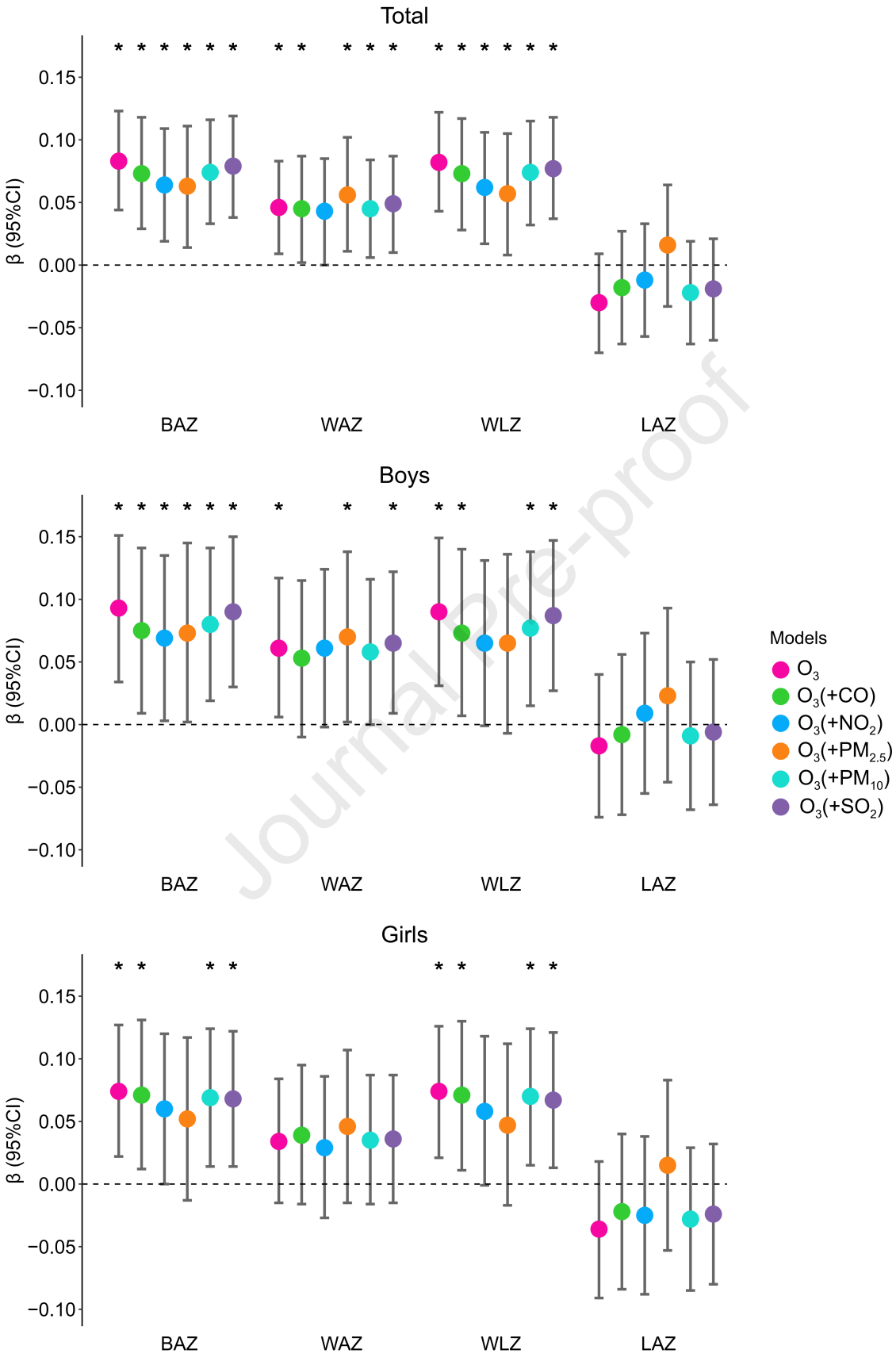

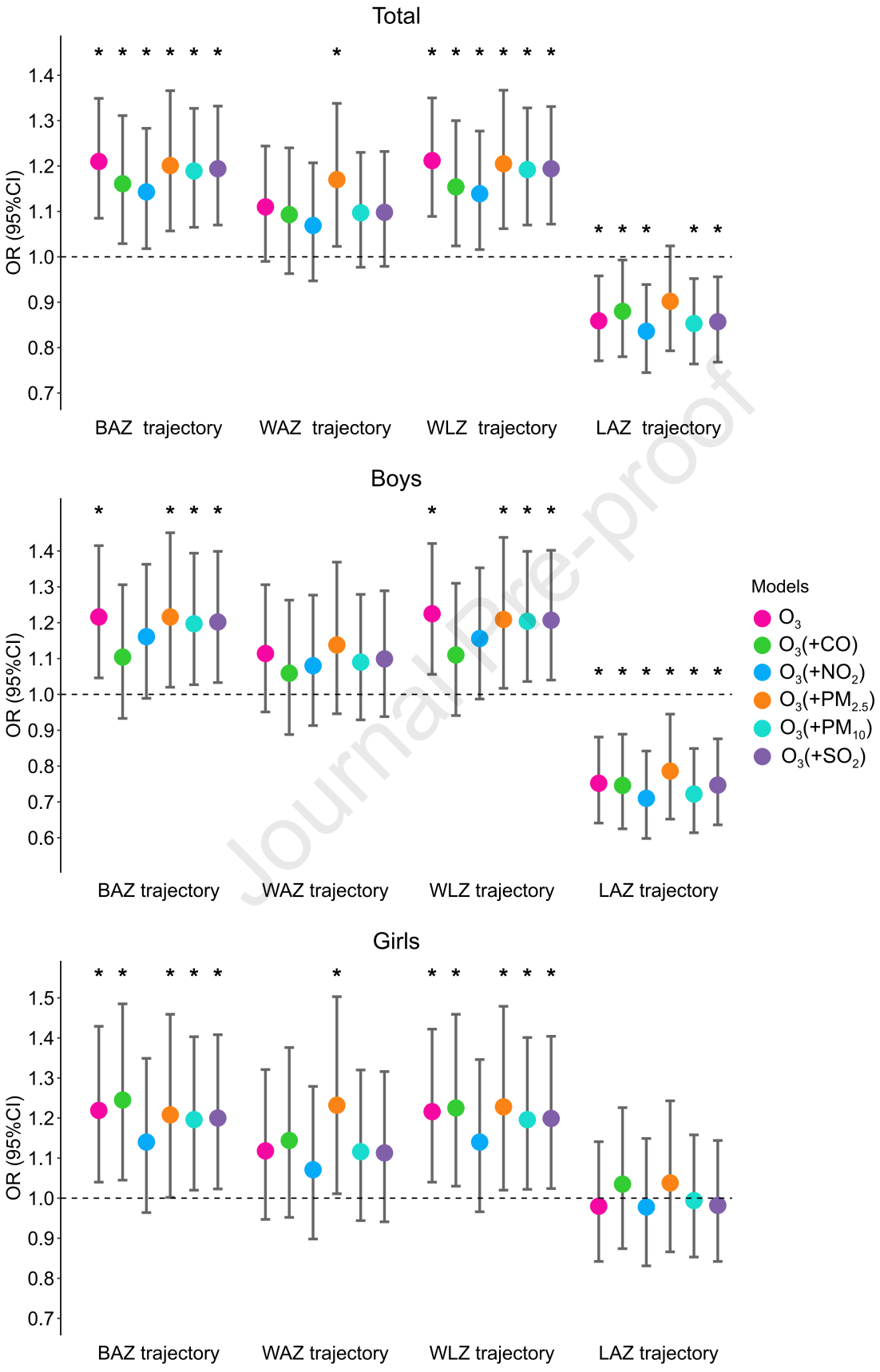

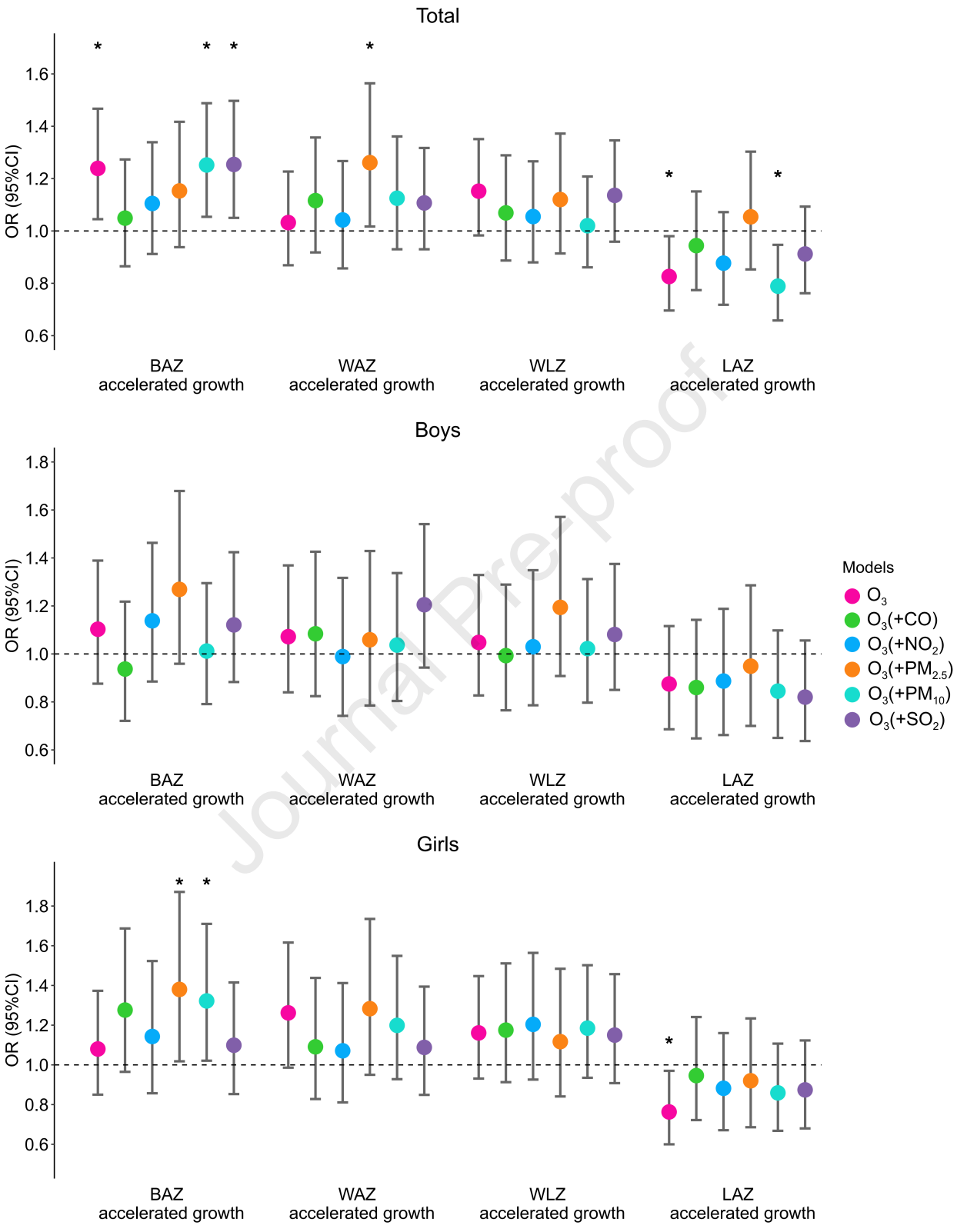

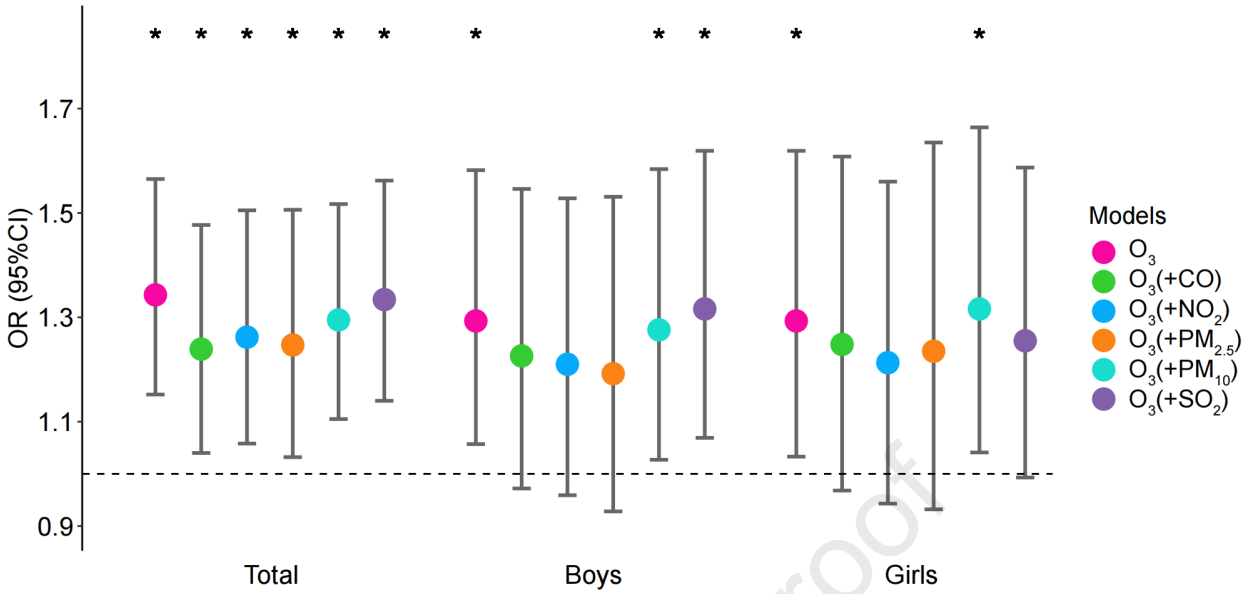

• A high-resolution ozone assessment model was used to access individual prenatal ozone exposure instead of relying on fixed monitoring stations.

• Prenatal exposure to ozone was positively associated with children growth trajectories.

• Prenatal ozone may increase the risk of overweight and obesity in children for the first 2 years