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Outdoor air pollution and hormone-assessed pubertal development in children: Results from the GINIplus and LISA birth cohorts

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ABSTRACT

Background: Air pollution is hypothesized to affect pubertal development. However, the few studies on this topic yielded overall mixed results. These studies did not consider important pollutants like ozone, and none of them involved pubertal development assessed by estradiol and testosterone measurements. We aimed to analyze associations between long-term exposure to four pollutants and pubertal development based on sex hormone concentrations among 10-year-old children.

Methods: These cross-sectional analyses were based on the 10-year follow-up medical examinations of 1945 children from the Munich and Wesel centers of the GINIplus and LISA German birth cohorts. Female and male pubertal development was assessed by dichotomizing the concentration of hormones in serum at 18.4 pmol/L and 0.087 nmol/L using the lower limits of quantification for estradiol and testosterone, respectively. Land-use regression models derived annual average concentrations of particulate matter with an aerodynamic diameter $<$ 2.5 and 10 μm ($PM_{2.5}$ and PM_{10}), as well as spatial models assessed yearly average concentrations of nitrogen dioxide (NO_2) and ozone, were calculated at the 10-year residential addresses. To evaluate associations, we utilized logistic regressions adjusted for potential covariates. The analyses were stratified by area and sex.

Results: Around 73% of the 943 females and 25% of the 1002 males had a high level of hormones and had already started puberty at the age of 10. Overall, we found no statistically significant associations between exposure to particles ($PM_{2.5}$ or PM_{10}) and pubertal development. Results on NO_2 and ozone were not significant as well; for

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Abbreviations: BMI, body mass index; CI, confidence interval; CV, coefficient of variation; EDCs, endocrine disrupting chemicals; ELAPSE, Effects of Low-Level Air Pollution: A Study in Europe; ESCAPE, European Study of Cohorts for Air Pollution Effects; GAM, generalized additive model; GINIplus, German Infant study on the influence of a Nutritional Intervention plus environmental and genetic influences on allergy development; IQR, interquartile range; LISA, influence of Lifestyle factors on the development of the Immune System and Allergies in East and West Germany; LUR, land-use regression; NO_2, nitrogen dioxide; OR, odds ratio; PM, particulate matter; $PM_{2.5}$, particulate matter with an aerodynamic diameter $<$ 2.5 μm; PM_{10}, particulate matter with an aerodynamic diameter $<$ 10 μm; ppb, parts per billion; SD, standard deviation.

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instance, per 10 μg/m^3 increase in ozone concentration, odds ratios and 95% confidence intervals were 0.900 (0.605, 1.339) and 0.830 (0.573, 1.203) for females and males, respectively. Stratified by area, the aforementioned results did not reveal any associations either.

Conclusions: Our study did not observe the associations between ambient air pollutants and pubertal development determined by estradiol and testosterone levels in children. However, due to the current limited number of studies on this topic, our results should be cautiously interpreted. Future longitudinal studies are needed to assess the association.

1. Introduction

Sex hormones trigger pubertal development. Abnormalities in this process might be linked to detrimental health outcomes, including respiratory illness (Lieberoth et al., 2015) and allergies (Zurawiecka and Wronka, 2019), cardiovascular disease (Canoy et al., 2015; Day et al., 2015), and diabetes (Day et al., 2015; Janghorbani et al., 2014), as well as psychological disorders (Joinson et al., 2011; Natsuaki et al., 2011) and cancer (Day et al., 2017; Okasha et al., 2003).

Air pollution, among many factors, is postulated to play a role in the dysregulation of hormones (Kim et al., 2020; Lin et al., 2019; Miller et al., 2016; Radwan et al., 2016), and therefore, it might be a risk factor for abnormal pubertal development. Apart from existing studies on harmful substances, highlighting the role of environmental endocrine disrupting chemicals (EDCs) on pubertal development (Özen and Darcan, 2011; Parent et al., 2015; Windham et al., 2015; Wolff et al., 2015), a small number of studies uncovered that other typical pollutants like particulate matter (PM) or nitrogen dioxide (NO_2) might contribute to the precocious or delayed onset of puberty (Huang et al., 2017; Jung et al., 2018; McGuinn et al., 2016).

Currently, there are only a few epidemiological studies investigating air pollution and pubertal development (Huang et al., 2017; Jung et al., 2018; McGuinn et al., 2016). These studies were based on clinical inspection or self-reported pubertal development, and the stemming results are heterogeneous in general. It is noteworthy that so far, no analyses on air pollution and pubertal development were based on sex hormone measurements; also, none of the published studies explored the association with exposure to ambient ozone.

The present study, therefore, aimed to shed light on the association between long-term exposure to PM with an aerodynamic diameter < 10 μm (PM_{10}) or < 2.5 μm ($PM_{2.5}$), NO_2, as well as ozone, and pubertal development. The onset of puberty was assessed on the basis of two main sex hormones, estradiol in females and testosterone in males, among 10–year-old children from two areas in Germany.

2. Material and methods

2.1. Study population

The study population was selected based on two population-based German birth cohorts “German Infant study on the influence of a Nutritional Intervention plus environmental and genetic influences on allergy development” (GINIplus) and “influence of Lifestyle factors on the development of the Immune System and Allergies in East and West Germany” (LISA). The cohorts recruited only healthy newborns delivered between 1995 and 1999 at a full gestational age (≥37 weeks) and with a normal birth weight (>2500 g). Totally, 2949 participants from Munich and 3042 participants from Wesel were enrolled in the GINIplus cohort. For the LISA cohort, 1464 participants were recruited from Munich, and 348, 976, and 306 from Wesel, Leipzig, and Bad Honnef, respectively. Ethical approval of the studies was acquired from the local ethics committees (Bavarian Board of Physicians, Board of Physicians of North-Rhine-Westphalia, and University of Leipzig). Written informed consent was signed by the legal guardians of the participants. Details on both cohorts can be accessed elsewhere (Heinrich et al., 2002; von Berg et al., 2010; Zutavern et al., 2006).

We selected the study population among the participants residing in Munich and Wesel, living at the current address for at least one year, and with complete information on pollutant exposure and hormone measurements from the follow-up at 10 years of age (Fig. 1). As data collection was harmonized, the data from the two cohorts were pooled as in previous analyses (Harris et al., 2017; Zhao et al., 2019b).

2.2. Outcome characterization

At the 10-year follow-up, the children participated in physical examinations, including blood sampling between the years 2005 and 2009. During the examination, the venous blood of the participants was sampled into serum separator tubes. After centrifuging, the serum was stored at −80 °C.

The serum concentration of testosterone and estradiol was measured by the mechanized immunoassay system Modular (Roche, Germany). Regarding analytical sensitivity, the lower limits of quantification were 18.4 pmol/L for estradiol and 0.087 nmol/L for testosterone. Intra- and inter-assay coefficients of variation (CVs) for estradiol measurements were lower than 5.29% for a concentration of 378 pmol/L and lower than 3.56% for 1941 pmol/L, respectively; For testosterone, intra- and inter-assay CVs were below 4.06% for a concentration of 6.2 nmol/L and 2.83% for 20.2 nmol/L, respectively (Kohlboeck et al., 2014).

There were 696 out of 943 females with hormone concentrations higher than the lower limit of quantification, and for males, this figure was 248 out of 1002. We thus dichotomized both concentrations with reference to the aforementioned values (estradiol > 18.4 pmol/L in females; testosterone > 0.087 nmol/L in males) as we have done previously (Harris et al., 2017; Zhao et al., 2019a).

2.3. Assessment of ambient air pollution exposure

Annual average concentrations (μg/m^3) of PM_{10} and $PM_{2.5}$ were estimated by area-specific land-use regression (LUR) models initially developed within the “European Study of Cohorts for Air Pollution Effects” (ESCAPE, www.escapeproject.eu) (Beelen et al., 2013; Eeftens et al., 2012). In brief, between October 2008 and November 2009, PM_{10} and $PM_{2.5}$ concentrations were monitored by 20 air measuring stations for three consecutive two-week measurement periods in both Munich and Wesel. Annual averages of PM at measurement sites were calculated based on averages of the three measurements, and temporal variation was accounted for using data from yearly-operating background measuring stations (one per area). Population, traffic data, and land use were included in building area-specific LUR models to estimate PM pollution at the residential address of each participant. Models’ explained variance ranged from 0.78 to 0.97.

Given that ozone was not measured and modeled within the ESCAPE project, annual mean concentrations (μg/m^3) of ozone and its precursor pollutant NO_2 were derived from the ELAPSE (Effects of Low-Level Air Pollution: A Study in Europe, www.elapseproject.eu) study (de Hoogh et al., 2018). Briefly, West-European LUR models at a 100 m × 100 m spatial scale were generated based on the European Environmental Agency AirBase monitoring data, and also incorporated satellite observations, chemical transport model data, as well as land use and traffic predictors, and further improved with kriging models. Models’ explained variation in the measured concentration varied from 0.54 to

0.83. As ozone concentrations are highly variable, the annual mean concentration was calculated as an average of daily maximum running 8-hour average concentration, whereas NO_2 was estimated as an annual average. We extrapolated these concentrations over the 2005 – 2009 period.

The aforementioned long-term exposure to PM_{10}, $PM_{2.5}$, NO_2, and ozone was estimated at geocoded residential addresses of the participants at 10 years of age. The assignment of air pollution estimates was conducted in ArcGIS Geographical Information System (version 10.4, ESRI, Redlands, CA).

2.4. Covariates

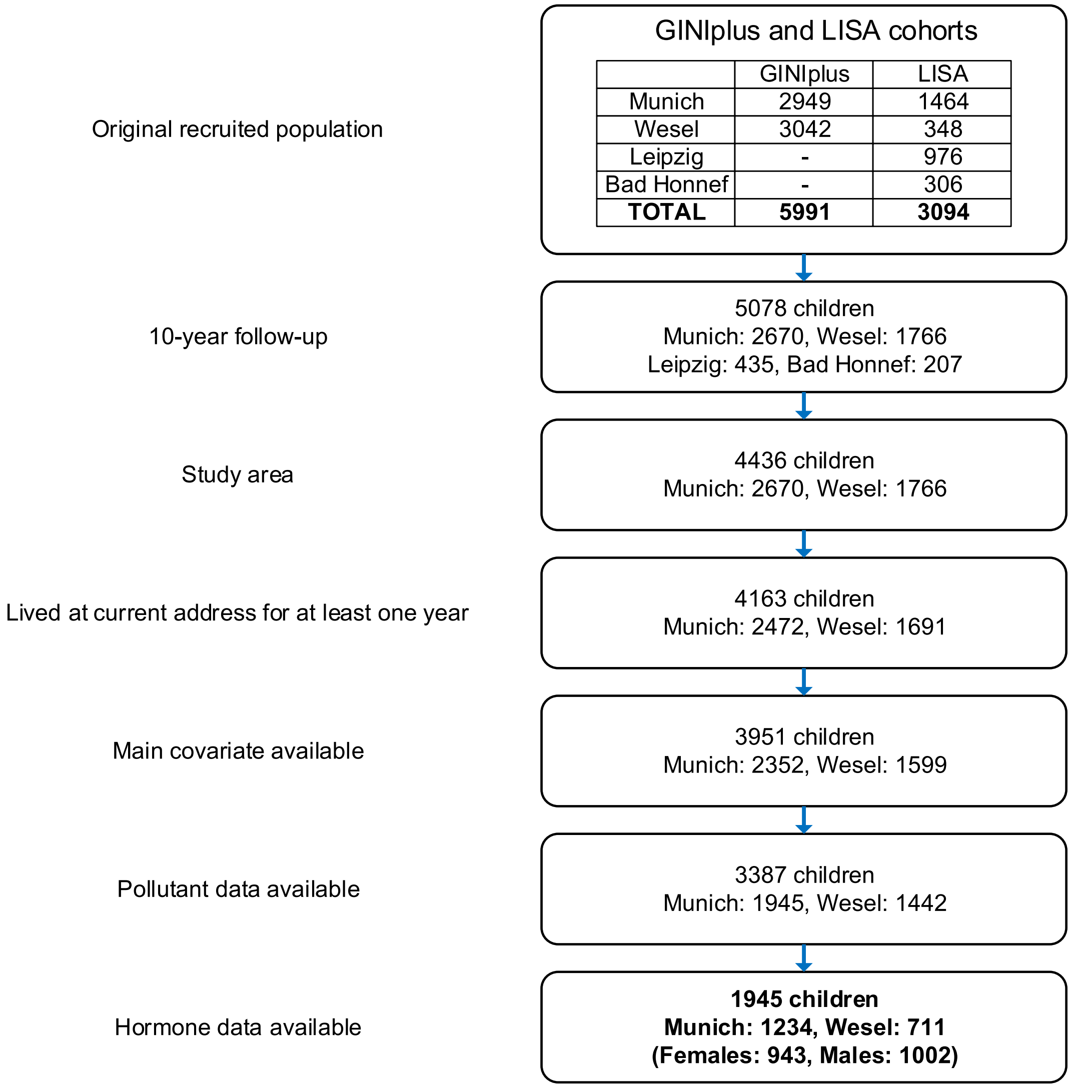
Besides basic factors, namely sex (female, male), exact age at the follow-up visit, and body mass index (BMI, kg/m^2), we considered other relevant covariates for the present study, by reference to the previous research on environmental exposure and endocrine effect (Thiering et al., 2016).

Regarding lifestyle factors, we considered second-hand smoke exposure (never, likely never, or ever from birth until age 10), time spent in front of a screen like a computer or television (high: $\geq$ 1 hour/day in summer or $\geq$ 2 hours/day in winter), time spent outside (high: $\geq$ 4 hours/day in summer or $\geq$ 2 hours/day in winter), physical activity level (low, medium and high were defined as moderate physical activity $<$ 7 hours per week, moderate physical activity $\geq$ 7 hours and $<$ 10.5 hours per week, moderate physical activity $\geq$ 10.5 hours per week, alternatively vigorous physical activity $\geq$ 3.5 hours per week, respectively (Janssen, 2007)). Considering family circumstances, the following factors were involved: maternal smoking during pregnancy (yes/no), maternal age at birth ($\leq$30 years, 30–35 years, $>$ 35 years), parental education (based on the highest number of years of school education reported by either parent; low, medium and high were respectively defined as $<$ 10 years, $=$ 10 years, and $>$ 10 years), together with single-parent family status (yes/no) and net equivalent household income (area-specific tertiles) at 10 years.

Additionally, we included covariates on technical details of the physical examinations: season (warm: April to October; cold: November to March), day time (8:00–11:00, 11.01–14:00, 14:01–19:00), and fasting state (yes/no) of the blood sampling.

2.5. Statistical analysis

We utilized the Chi-square test and Student's t-test to examine the differences between the analytic sample and the original population, as well as the two selected samples from Munich and Wesel. The Wilcoxon test was used to examine the differences between pollutants across study



	GINIplus	LISA
Munich	2949	1464
Wesel	3042	348
Leipzig	-	976
Bad Honnef	-	306
TOTAL	**5991**	**3094**

Fig. 1. Flow chart for participant selection with inclusion criteria. Note: Pollutant data available: PM10, PM2.5, NO2, and ozone. Main covariate available: body mass index.

areas.

The relationship between pollutants and the pubertal development did not strongly deviate from linearity, as tested by generalized additive models (GAMs, Hastie and Tibshirani, 1986); thus, pollutant data were considered as continuous variables in logistic regression. Our adjusted model was determined after including the above-mentioned covariates (subsection 2.4.). Crude models without any adjustments were built as well.

For each pollutant, all the analyses were conducted for the combined study population from two areas and for Munich and Wesel separately. Additionally, two-pollutant models, including simultaneously two less correlated pollutants (Spearman correlation coefficient < 0.7, Figure S1), were constructed for sensitivity analysis. The results of our analyses are presented as odds ratios (ORs) with 95% confidence intervals (CIs) scaled by 10 μg/m^3 increase in pollution concentration.

All analyses were conducted in R 3.5.2 (R Core Team, 2018). GAMs were fitted by *gam* function from the *mgcv* package (Wood, 2011). We considered a significance level of 0.05 in all our analyses.

3. Results

3.1. Characteristics of participants

Our selected samples included 943 females and 1002 males aged 10 years (Fig. 1, Table 1).

Considering the differences between the analytic sample and the

Table 1

Characteristics of study populations.

Variable	Category	Females			Males		
		All n (%)	Munich n (%)	Wesel n (%)	All n (%)	Munich n (%)	Wesel n (%)
Study	GINIplus observation	355 (37.6)	177 (30.1)	178 (50.1)	339 (33.8)	177 (27.2)	162 (46.0)
	GINIplus intervention	352 (37.6)	216 (36.7)	136 (38.3)	369 (36.8)	229 (35.2)	140 (39.8)
	LISA	236 (25.0)	195 (33.2)	41 (11.5)	294 (29.3)	244 (37.5)	50 (14.2)
Age	years (Mean ± SD)	10.05 ± 0.17	10.04 ± 0.20	10.06 ± 0.11	10.04 ± 0.17	10.04 ± 0.20	10.05 ± 0.11
BMI	kg/m^2 (Mean ± SD)	17.35 ± 2.52	16.99 ± 2.32	17.93 ± 2.73	17.35 ± 2.39	17.02 ± 2.19	17.96 ± 2.61
Time spent outside [a]	High	162 (17.2)	75 (12.8)	87 (24.5)	205 (20.5)	83 (12.8)	122 (34.7)
	Low	766 (81.2)	506 (86.1)	260 (73.2)	782 (78.0)	557 (85.7)	225 (63.9)
	Missing	15 (1.6)	7 (1.2)	8 (2.3)	15 (1.5)	10 (1.5)	5 (1.4)
Time in front of a screen [b]	High	253 (24.9)	102 (17.3)	133 (37.5)	366 (36.5)	200 (30.8)	166 (47.2)
	Low	708 (75.1)	486 (82.7)	222 (62.5)	636 (63.5)	450 (69.2)	186 (52.8)
Physical activity [c]	High	257 (27.3)	136 (23.1)	121 (34.1)	421 (42.0)	249 (38.3)	172 (48.9)
	Medium	270 (28.6)	174 (29.6)	96 (27.0)	251 (25.0)	165 (25.4)	86 (24.4)
	Low	154 (26.9)	186 (31.6)	68 (19.2)	192 (19.2)	145 (22.3)	47 (13.4)
	Missing	162 (17.2)	92 (15.6)	70 (19.7)	138 (13.8)	91 (14.0)	47 (13.4)
Parental education [d]	High (>10 years)	614 (65.1)	452 (76.9)	162 (45.6)	639 (63.8)	491 (75.5)	148 (42.0)
	Medium (=10 years)	164 (17.4)	75 (12.8)	89 (25.1)	177 (17.7)	86 (13.2)	91 (25.9)
	Low (<10 years)	165 (17.5)	61 (10.4)	104 (29.3)	186 (18.6)	73 (11.2)	113 (32.1)
Maternal age at birth	≤ 30 years	355 (37.6)	196 (33.3)	159 (44.8)	378 (37.7)	195 (30.0)	183 (52.0)
	> 30 to ≤ 35 years	425 (45.1)	272 (46.3)	153 (43.1)	437 (43.6)	302 (46.5)	135 (38.4)
	> 35 years	163 (17.3)	120 (20.4)	43 (12.1)	187 (18.7)	153 (23.5)	34 (9.7)
Single parent	Yes	91 (9.7)	68 (11.6)	23 (6.5)	107 (10.7)	84 (12.9)	23 (6.5)
	No	841 (89.2)	512 (87.1)	329 (92.7)	884 (88.2)	557 (85.7)	327 (92.9)
	Missing	11 (1.2)	8 (1.4)	3 (0.8)	11 (1.1)	9 (1.4)	2 (0.6)
Smoking exposure	During pregnancy	122 (12.9)	65 (11.1)	57 (16.1)	121 (12.1)	79 (12.2)	42 (11.9)
	between 0 and 10	363 (38.5)	181 (30.8)	182 (51.3)	373 (37.2)	196 (30.2)	177 (50.3)
Income [e]	High	262 (27.8)	174 (29.6)	88 (26.8)	312 (31.1)	197 (30.3)	115 (32.7)
	Medium	315 (33.4)	183 (31.1)	132 (37.2)	315 (31.4)	211 (32.5)	104 (29.5)
	Low	294 (31.2)	195 (33.2)	99 (27.9)	293 (29.2)	192 (29.5)	101 (28.7)
	Missing	72 (7.6)	36 (6.1)	36 (10.1)	82 (8.2)	50 (7.7)	32 (9.1)
Season of blood sampling [f]	Warm	582 (61.7)	358 (60.9)	224 (63.1)	653 (65.2)	411 (63.2)	242 (68.8)
	Cold	361 (38.3)	230 (39.1)	131 (36.9)	349 (34.8)	239 (36.8)	110 (31.2)
Time of blood sampling	8:00–11:00	279 (29.6)	210 (35.7)	69 (19.4)	273 (27.2)	207 (31.8)	66 (18.8)
	11:01–14:00	110 (11.7)	78 (13.3)	32 (9.0)	105 (10.5)	84 (12.9)	21 (6.0)
	14:01–19:00	511 (54.2)	279 (47.4)	232 (65.4)	587 (58.6)	336 (51.7)	251 (71.3)
	Missing	43 (4.6)	21 (3.6)	22 (6.2)	37 (3.7)	23 (3.5)	14 (4.0)
Fasting blood sample	Yes	188 (19.9)	145 (24.7)	43 (12.1)	153 (15.3)	126 (19.4)	27 (7.7)
	No	753 (79.9)	443 (75.3)	310 (87.3)	849 (84.7)	524 (80.6)	325 (92.3)
	Missing	2 (0.2)	0 (0.00)	2 (0.6)	0 (0.00)	0 (0.00)	0 (0.00)
Estradiol	pmol/L (Median; IQR)	34.80; 39.65	38.60; 42.62	30.00; 29.05	–	–	–
Testosterone	nmol/L (Median; IQR)	–	–	–	0.09; 0.00	0.09; 0.01	0.09; 0.00
Pubertal development (Puberty onset) [g]	Yes	696 (73.8)	457 (77.7)	239 (67.3)	248 (24.8)	164 (25.2)	84 (23.9)
	No	247 (26.2)	131 (22.3)	116 (32.7)	754 (75.2)	486 (74.8)	268 (76.1)
Total		943 (100.00)	588 (62.4)	355 (37.6)	1002 (100.00)	650 (64.9)	352 (35.1)

Note:

Abbreviations: BMI, body mass index; SD, standard deviation.

[a] High is defined as ≥ 4 hours per day in summer or ≥ 2 hours in winter.

[b] High is defined as ≥ 1 hour per day in summer or ≥ 2 hours per day in winter.

[c] Low, moderate physical activity < 7 h per week; medium, moderate physical activity ≥ 7 h and < 10.5 h per week; high, moderate physical activity ≥ 10.5 h per week or vigorous physical activity ≥ 3.5 h per week.

[d] Highest number of years of school education for either parent was calculated, based on the German education system.

[e] Net equivalent household income (€/month), according to area-specific tertiles.

[f] Warm, April to October; cold, November to March.

[g] Females, estradiol > 18.4 pmol/L; males, testosterone > 0.09 nmol/L.

Table 2
Descriptive characteristics of pollutants concentrations.

Pollutant	Index	All	Munich	Wesel
PM_{10} [a]	Mean	21.95	19.99	25.39
	SD	3.26	2.29	1.21
	Min	14.80	14.80	23.87
	Max	31.43	30.23	31.43
	Median	21.61	20.35	25.14
	IQR	4.91	2.91	1.51
$PM_{2.5}$ [a]	Mean	14.76	13.27	17.37
	SD	2.13	0.87	0.69
	Min	10.66	10.66	15.78
	Max	21.38	18.79	21.38
	Median	13.86	13.21	17.24
	IQR	4.00	1.01	0.80
NO_2 [b]	Mean	22.03	22.55	21.13
	SD	3.86	4.16	3.07
	Min	11.91	11.91	14.35
	Max	47.51	47.51	41.36
	Median	21.90	22.48	21.09
	IQR	4.16	4.44	3.31
Ozone [b]	Mean	69.18	71.08	65.85
	SD	4.90	4.94	2.42
	Min	49.33	49.33	51.41
	Max	83.82	83.82	70.77
	Median	68.77	71.58	65.88
	IQR	7.20	6.66	2.91

Note:
Abbreviation: SD, standard deviation; IQR, interquartile range.
[a] Annual average concentration in 2005–2009, derived from ESCAPE project, μg/m^3.
[b] Annual average concentration in 2005–2009, derived from ELAPSE project, μg/m^3.

original population, we found that the children of parents with high education were more likely to be included in the study sample (data not shown). Meanwhile, almost all characteristics differed between participants from Munich and Wesel. Specifically, children from Munich were significantly more likely to have a lower BMI, to spend less time outside, to have less physical activity, to be not exposed to passive smoking at home, and to have parents with higher educational levels (data not shown). These observations are in accordance with our previous analyses (Markevych et al., 2019; Zhao et al., 2019b).

Around 73% of 10-year-old females had estradiol concentrations above the threshold and had already entered puberty. The females from Munich had a significantly higher rate of onset of puberty than those from Wesel. Approximately 75% of the males had lower testosterone concentrations below the threshold at 10. They were thus still in the prepubertal stage.

3.2. Characteristics of pollutants

Table 2 presents the level of long-term air pollutants in different areas. In Munich, the median concentration of ozone was 71.58 μg/m^3, NO_2 was 22.48 μg/m^3, PM_{10} was 20.35 μg/m^3, and $PM_{2.5}$ was 13.21 μg/m^3. These values for Wesel were 65.88, 21.09, 25.14, and 17.24 μg/m^3, respectively. Munich participants were more likely to expose to gaseous pollutants like ozone, while Wesel participants tended to suffer from higher particulate pollution.

3.3. Associations between pollutants and pubertal development

The adjusted and crude ORs for the association between long-term exposure to air pollutants and pubertal development are shown in Table 3.

Overall, the effect estimates from the adjusted models went in different directions and were mainly not significant for the entire study population nor for the specific areas (Table 3). For instance, per 10 μg/m^3 increase in PM_{10} concentration, ORs and 95% CIs were 0.896 (0.379, 2.122) and 0.821 (0.383, 1.759) for females and males, respectively. Likewise, the effect effects of ozone were 0.900 (0.605, 1.339) for females and 0.830 (0.573, 1.203) for males. Within several subgroup

Table 3
Associations between pollutants and sex hormones from adjusted models and crude models.

Sex	Area	Pollutant	Adjusted OR (95% CI)	p-value	Crude OR, (95% CI)	p-value
Female	All	PM_{10}	0.896 (0.379, 2.122)	0.804	**0.515 (0.327, 0.812)**	**0.004**
		$PM_{2.5}$	0.163 (0.022, 1.166)	0.071	**0.278 (0.142, 0.544)**	**<0.001**
		NO_2	0.892 (0.581, 1.369)	0.600	0.996 (0.682, 1.457)	0.985
		Ozone	0.900 (0.605, 1.339)	0.604	1.261 (0.943, 1.688)	0.118
	Munich	PM_{10}	0.749 (0.275, 2.041)	0.572	0.984 (0.416, 2.327)	0.970
		$PM_{2.5}$	**0.026 (0.002, 0.300)**	**0.003**	0.120 (0.014, 1.061)	0.057
		NO_2	0.723 (0.428, 1.220)	0.225	0.850 (0.539, 1.338)	0.482
		Ozone	0.936 (0.598, 1.464)	0.771	0.944 (0.638, 1.396)	0.773
	Wesel	PM_{10}	0.863 (0.098, 7.616)	0.894	0.941 (0.142, 6.227)	0.949
		$PM_{2.5}$	1.330 (0.026, 67.338)	0.886	2.163 (0.073, 63.924)	0.655
		NO_2	1.189 (0.474, 2.987)	0.712	1.056 (0.499, 2.233)	0.886
		Ozone	0.636 (0.211, 1.923)	0.423	0.829 (0.326, 2.108)	0.694
Male	All	PM_{10}	0.821 (0.383, 1.759)	0.612	0.833 (0.537, 1.293)	0.416
		$PM_{2.5}$	1.089 (0.156, 7.605)	0.931	0.880 (0.445, 1.741)	0.713
		NO_2	1.152 (0.768, 1.728)	0.493	1.097 (0.761, 1.582)	0.620
		Ozone	0.830 (0.573, 1.203)	0.324	0.924 (0.684, 1.247)	0.603
	Munich	PM_{10}	0.858 (0.381, 1.934)	0.711	0.757 (0.353, 1.625)	0.476
		$PM_{2.5}$	0.682 (0.069, 6.787)	0.744	0.809 (0.103, 6.374)	0.840
		NO_2	1.211 (0.759, 1.933)	0.422	1.121 (0.731, 1.720)	0.600
		Ozone	0.820 (0.553, 1.218)	0.326	0.854 (0.596, 1.223)	0.389
	Wesel	PM_{10}	0.985, (0.094, 10.356)	0.990	0.892 (0.123, 6.476)	0.910
		$PM_{2.5}$	5.519 (0.105, 290.570)	0.398	3.318 (0.117, 94.160)	0.482
		NO_2	1.050 (0.421, 2.621)	0.916	0.956 (0.437, 2.088)	0.909
		Ozone	0.697 (0.218, 2.233)	0.544	0.934 (0.340, 2.562)	0.894

Note:
Abbreviation: CI, confidence interval; OR, odds ratio.
1. ORs and 95% CIs are scaled by an increase of 10 μg/m^3 of pollutants.
2. Adjusted model: all estimates were adjusted for the exact age, sex, body mass index, time spent outside and in front of a screen, physical activity level, season and time of the blood sampling, household income, and other variables listed in Table 1.
3. Crude model was not adjusted for any covariates.

analyses, one statistically significant association was detected for females in Munich: the increased PM concentration might delay the pubertal development or decrease the detectable testosterone estrogen levels. However, no such associations were observed for Wesel (Table 3). Although $PM_{2.5}$ exposure in Munich might be associated with a decreased estradiol level in girls, this isolated result was inconsistent across the study areas and thus should be interpreted with caution.

Regarding the crude models, the mixed results were not consistent either (Table 3). The size of the effect differed and some directions of the association even changed across different models. Similarly, we cannot observe robust associations from the two-pollutant models (Table S1).

4. Discussion

4.1. Main study findings

Based on the results of our analysis in 943 German females and 1002 males aged 10 years, there is no indication that air pollution can affect puberty onset as determined by estradiol and testosterone levels.

4.2. Interpretations and comparisons with other studies

There is a handful of published studies on pubertal development in relation to air pollution. The results from two studies that used Tanner scale assessment of puberty are not in line with each other. McGuinn et al. (2016) analyzed 437 American girls with exposure to traffic-related air pollution from the CYGNET study. Girls with higher residential proximity to traffic were found to reach one pubertal stage 2–9 months earlier than those with low exposure. On the contrary, among 1,938 girls and 2,136 boys from the Hong Kong's "Children of 1997" birth cohort, Huang et al. (2017) found that PM_{10} exposure in utero and during infancy was associated with delayed female puberty, whereas sulfur dioxide and NO_2 exposure in utero, during infancy, and in childhood were associated with postponed male puberty onset. In addition, Jung et al. (2018) investigated the association between PM_{10} exposure and self-reported age at menarche among 639 girls aged 13–17 years from South Korea. This study also suggested that an elevated PM_{10} concentration may decrease the age of menarche, resulting in advanced pubertal development in females.

Generally, the heterogeneous results of these studies may be caused by the differences in study design, population characteristics, outcome definitions, and study confounding like socioeconomic status, as well as exposure metrics, windows, and levels. Specifically, regarding PM_{10} and pubertal onset, we found no association, while results from two previous studies (Huang et al., 2017; Jung et al., 2018) point at two distinct directions – pubertal developments can be delayed or advanced.

In terms of the exposure level of PM_{10}, the two aforementioned East Asian studies (Huang et al., 2017; Jung et al., 2018) reported a mean PM_{10} concentration of more than 56.07 $\mu g/m^3$. In the present study, we have a much lower mean concentration of 21.95 $\mu g/m^3$. Although the linearity test between exposure and outcome was passed within our range of PM_{10} concentration, the dose–response relationship might be different at higher PM_{10} levels.

In terms of the characteristics of PM_{10}, the size and density of PM *per se* (Deng et al., 2019) are relevant to its health effects. In addition to the physical features, compositions of PM may count more.PM contains various microscopic solids or liquid droplets, and EDCs could be involved as an ingredient (Salgueiro-González et al., 2015). It is known that the effects of EDCs on pubertal development are sexually dimorphic, (exposure) window-characteristic, and compound-specific (Greenspan and Lee, 2018) – endocrine disrupters, like phthalates, phenols, or heavy metals, can be associated with both precocious and delayed pubertal development (Iavicoli et al., 2009; Özen and Darcan, 2011; Windham et al., 2015; Wolff et al., 2015). Therefore, even if the exposure levels were identical, PM may not, or would either trigger or defer the pubertal development, depending on the area-specifically embodied EDCs.

To the best of our knowledge, no previous studies investigated the association between air pollutants and pubertal onset defined based on (dichotomized) levels of estradiol and testosterone in children; therefore, we cannot compare the non-significant association observed between the four pollutants and estradiol or testosterone in the present study with others. Even if we take a look at the association – air pollution and estradiol or testosterone – investigated among adults or examined in other species, we see only a few studies with different designs investigated this topic and yielded heterogeneous results, either epidemiologically (Radwan et al., 2016; Wenger et al., 2009) or experimentally (Angoa-Pérez et al., 2006; Bourdon et al., 2018; Durrani et al., 2012; Fuentes et al., 2019; Guevara-Guzmán et al., 2009; Shi et al., 2016; Sobolewski et al., 2018).

4.3. Possible mechanisms

Many studies have suggested that air pollution may impact the hypothalamic–pituitaryadrenal axis (Rose et al., 2020; Thomson et al., 2019) and alter the level of stress hormones like cortisol (Miller et al., 2016; Tomei et al., 2003; Wing et al., 2018). Consequently, one may reasonably hypothesize that the typical air pollutants may have an impact on estradiol or testosterone through similar pathways or mechanisms connecting air pollution with other hormones.

Beyond the well-established role of endocrine disruptors mimicking normal hormones (Annamalai and Namasivayam, 2015; Darbre, 2018), the mechanisms linking air pollution and pubertal development or sex hormones are still under-investigated.

As for the gaseous pollutants, whilst no epidemiological studies explored sex hormones in relation to NO_2 exposure, results from rat models reveal that NO_2 exposure was associated with an increase in the airways amine precursor uptake decarboxylase cells (Kleinerman et al., 1981) and argyrophilic cells (Marchevsky and Kleinerman, 1982), also known as neuroendocrine cells. These types of cells facilitate neuroendocrine integration and might alter the sex hormones level (Evsyukova, 2006). In addition, nitric oxide metabolized from nitrate or nitrite might reduce gonadal steroidogenesis, according to *in vitro* and *in vivo* studies (Panesar and Chan, 2000).

Likewise, the association between ozone exposure and sex hormones has been analyzed using mouse models: the testosterone levels in serum were decreased after ozone exposure, yet there was no significant variance in 17-β-estradiol levels (Shi et al., 2016). Additionally, recent findings from animal studies with exposure to ozone suggest that circulating hormone levels can mediate inflammatory responses: 17-β-estradiol can augment the necrosis and inflammation markers in rats (Chalfant and Bernd, 2014), and increases ozone-induced inflammation and airway hyperresponsiveness in female mice but not in males (Fuentes et al., 2019). The above suggests that the mechanisms linking ozone exposure to hormonal imbalance may be independent of the inflammatory pathway.

4.4. Limitations and strengths

The present study should be understood in light of its potential limitations. The hormone concentrations had to be dichotomized due to the skewed distribution and the lower limits of quantification. This might decrease statistical power and possibly mirror physiological pubertal development somewhat less well. Also, in line with other birth cohorts (Bornehag et al., 2012; MAL-ED Network Investigators, 2017), participants with low socioeconomic status were under-recruited and more often dropped out before follow-up, which might limit the external validity of our findings. Unfortunately, we could not adjust our analysis for area-level socioeconomic status, due to a lack of fine-resolution area-level social statistics. Furthermore, the cross-sectional design limits our ability to establish causality, which should, however, not be a big issue with environmental exposure and a physiological outcome. Another limitation of our study is the relatively short exposure period, covering only one year. As existing literature (Huang et al., 2017) indicates associations between exposure to air pollution during early life and pubertal onset, a prospective cohort study with repeated measurements, concerning prenatal, infancy, and childhood stages is warranted to pinpoint relevant exposure windows.

Beyond a relatively large study sample stemming from two birth cohorts, our study exhibits further strengths. Firstly, our air pollution data were abstracted within two European projects and correspond well to measurements. Secondly, compared with the Tanner stage relying on inspection and anthropometric measurements, or the age at menarche reported by participants, our measured hormone concentrations and the hormone-based onset of puberty have minor recall bias as well as less outcome misclassification. Thirdly, many relevant covariates, including BMI, time spent outdoors, physical activity, and second-hand smoking exposure, were available for adjustment. Altogether, relying on the robust models we constructed, we had the chance to pave the way for future investigations of the associations between exposure to $PM_{2.5}$ together with ozone and pubertal development or sex hormones in children.

5. Conclusions

We observed no significant associations between air pollutants and pubertal development defined by levels of estradiol and testosterone, although the association is biologically plausible. However, the associations should be further analyzed by detailed longitudinal studies, including repeated high sensitivity hormone measurements.

CRediT authorship contribution statement

Tianyu Zhao: Conceptualization, Data curation, Formal analysis, Methodology, Software, Visualization, Writing - original draft, Writing - review & editing. **Kai Triebner:** Methodology, Writing - review & editing. **Iana Markevych:** Methodology, Software, Writing - review & editing. **Marie Standl:** Methodology, Writing - review & editing. **Hicran Altug:** Software, Writing - review & editing. **Kees Hoogh:** Writing - review & editing. **Tamara Schikowski:** Writing - review & editing. **Dietrich Berdel:** Writing - review & editing. **Sibylle Koletzko:** Writing - review & editing. **Carl-Peter Bauer:** Writing - review & editing. **Andrea Berg:** Writing - review & editing. **Dennis Nowak:** Writing - review & editing. **Joachim Heinrich:** Conceptualization, Methodology, Supervision, Writing - review & editing.

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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The GINIplus Study group consists of the following: Institute of Epidemiology, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg (Heinrich J, Brüske I, Schulz H, Flexeder C, Zeller C, Standl M, Schnappinger M, Ferland M, Thiering E, Tiesler C); Department of Pediatrics, Marien-Hospital, Wesel (Berdel D, von Berg A); Ludwig-Maximilians-University of Munich, Dr von Hauner Children's Hospital (Koletzko S); Child and Adolescent Medicine, University Hospital rechts der Isar of the Technical University Munich (Bauer CP, Hoffmann U); IUF- Environmental Health Research Institute, Düsseldorf (Schikowski T, Link E, Klümper C, Krämer U, Sugiri D).

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Appendix A. Supplementary data

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