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Air pollution during infancy and lung function development into adolescence: The GINIplus/LISA birth cohorts study

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ABSTRACT

Background: Limited evidence exists on how air pollution exposure during infancy, i.e. the first year of life, may affect lung function development into adolescence.
Objectives: To investigate the association between exposure to air pollution during the first-year of life and lung function development up to the age of 15 in Germany.
Methods: We investigated 915 children from the GINIplus and LISA birth cohorts from Munich (n = 181) and Wesel (n = 734), who had at least two spirometric measurements at ages 6, 10 and 15. Z-scores of forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) were calculated. Annual average concentrations of nitrogen dioxide, particulate matter with diameters <2.5, <10 and 2.5–10 μm ($PM_{2.5/10/coarse}$), and $PM_{2.5}$ absorbance at home addresses during the first-year of life, were estimated by land-use regression models. Associations between infancy exposure and lung function changes were fitted using multivariable linear mixed models with adjustment for potential confounders.
Results: For per interquartile range increase in air pollutants during the first-year life, FEV_1 z-scores declined annually by −0.012 (95% confidence interval (CI): −0.014, −0.009) for $PM_{2.5}$ to −0.023 (95%CI: −0.028, −0.018) for PM_{coarse}. The declines in FVC were lower than FEV_1 [−0.006 (95%CI: −0.008, −0.003) to −0.011 (95%CI: −0.019, −0.003)]. In Munich, the attenuations were only significant for FEV_1. Effect estimates of infancy exposure for certain air pollutants were higher for groups with asthma, older maternal age, and breastfeeding <12 weeks than their counterparts.
Discussion: Infancy exposure to higher air pollution may reduce lung function development up to adolescence, with airway size more affected than lung volume restriction. The potential modifying effects of maternal age, asthmatic status of children and breastfeeding warrant further exploration.

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1. Introduction

The World Health Organization (WHO) estimates that the majority of children are living in an environment with air pollution concentrations above its guideline (WHO 2018). Exposure to air pollution is increasingly reported as a threat for respiratory health of children, which can limit lung function growth (Milanzi et al. 2018). Reduced lung function in adolescence has been associated with cardiorespiratory morbidity and mortality in later life, including chronic obstructive pulmonary disease, coronary artery disease and stroke (Young et al. 2007). To develop health promotion strategies and reduce the relevant health burden, it is essential to systematically clarify the adverse effect of air pollution on lung function development of children.

Many studies have shown that exposure to air pollution in early life may influence a variety of health outcomes, such as asthma prevalence and rhinitis, with adverse effects persisting up to adolescence or even later (Clark et al., 2010; Gehring et al., 2015). However, evidence of the impact of air pollution on paediatric lung function is mainly based on cross-sectional studies (Fuertes et al., 2015; Gehring et al., 2013; Knibbs et al., 2018; Usemann et al., 2019). For example, in Australia, per interquartile range (IQR) increase in outdoor nitrogen dioxide (NO_2) in the past 12 months was associated with 1.35% decline in forced expiratory volume in one second (FEV_1) and a 1.19% decline in forced vital capacity (FVC) in children aged 7–11 years (Knibbs et al. 2018). In Europe, higher levels of air pollutants at the current address were also associated with impaired lung function in children aged 6–8 years (Gehring et al. 2013). Only a few longitudinal studies have examined whether air pollution exposure during infancy affects paediatric lung function development, and these findings were inconsistent (Cai et al., 2020; Milanzi et al., 2018; Schultz et al., 2016).

In the current study, we investigated the effect of exposure to air pollution during the first year of life on lung function development from the age of 6 to 15 years. For the purpose of this study, we used data from two German multicentre population-based prospective birth cohorts launched in 1995. In addition, to identify vulnerable groups, we explored the modifying effect of factors on the association of interest, such as breastfeeding and maternal age, which have been associated with lung function development in previous studies.

2. Methods

2.1. Study population

The German Infant study on the influence of Nutrition Intervention plus environmental and genetic influences on allergy development (GINIplus) birth cohort recruited 5991 children from 09/1995–06/1998 in two German regions – Munich (South-East) and Wesel (North-West). Questionnaires were used to collect data on families' socio-demographics, lifestyle, children's environmental exposures, and parental and children's health conditions annually between the ages of 1 and 4 years, and at ages 6, 10 and 15 years. Spirometric measurements were performed for a subgroup of participants at ages 6, 10 or 15 years. The Influence of Life style factors on the development of the Immune System and Allergies in East and West Germany (LISA) birth cohort recruited 3094 children from 11/1997–01/1999 in four regions – Munich, Wesel, Leipzig (East) and Bad Honnef (North-West).

The two cohorts had harmonised designs at later follow-ups, and therefore were pooled for the same region for analysis (Heinrich et al., 2012; von Berg et al., 2010). The analytic sample was restricted to 734 children from Wesel and 181 children from Munich, who had high-quality spirometric measurements at two or three time-points during the 15-year follow-up (n = 915 together, see Fig. 1). All subjects are full-term children with normal birth weight.

Both cohorts have been approved by the local Ethics Committees with written consent signed by all parents of participants.

2.2. Assessment of lung function

Spirometric measurements (FEV_1 and FVC) were performed by trained personnel following the guidelines of the American Thoracic Society/European Respiratory Society. Detailed operation procedure of lung function measurements has been described elsewhere (Fuertes et al. 2015). To compare the impacts of air pollution on FEV_1 and FVC, and to assess how paediatric lung function may deviate from the general German children, measurements of the two indices were converted into z-scores using LUng function NOrmal values for KIDs in Germany (LUNOKID). The LUNOKID study was designed to provide reliable reference values of spirometry for German children and adolescents with

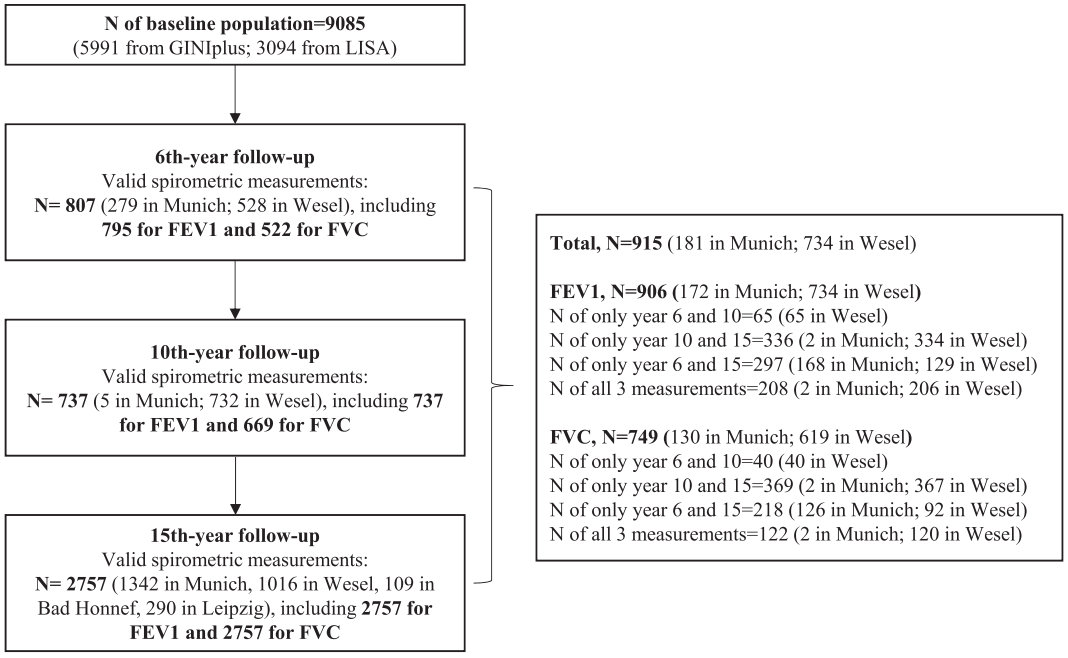

Fig. 1. Flowchart of population recruited in this study.

adjustment for the non-linear effects of age, height and sex (Hüls et al., 2013, 2016; Müller-Brandes et al., 2014).

2.3. Assessment of air pollution exposure

The annual average concentrations of NO_2, particulate matter with diameters <2.5, <10 and 2.5–10 μm ($PM_{2.5/10/coarse}$), and $PM_{2.5}$ absorbance at the home address in the first year of life (1995–1999) were assigned within the European Study of Cohorts for Air Pollution Effects (ESCAPE, www.escapeproject.eu). Details of measurements have been described elsewhere (Beelen et al., 2013; Cyrys et al., 2012; Eeftens et al., 2012a, 2012b). Briefly, between 10/2008–11/2009, $PM_{2.5/10}$ and $PM_{2.5}$ absorbance were measured from 20 monitoring sites and NO_2 were measured from 40 sites in both regions. The concentration of PM_{coarse} was calculated by subtracting $PM_{2.5}$ from PM_{10}. For each site, the 14-day measurements were performed during three periods (cold, warm and intermediate seasons), the data of which were averaged to get the site-specific annual average concentration. Land use regression (LUR) models were developed to predict the air pollution concentrations at the home addresses using predictors derived from geographic information systems, e.g., nearby traffic, population density, and land use. Exposure data from the first year of life were back-extrapolated: for each region, a central reference monitoring station was selected, which had continuous measurements throughout the years. The absolute temporal difference (for $PM_{2.5}$ and PM_{10}) or ratio ($PM_{2.5}$ absorbance, PM_{coarse} and NO_2) in air pollution concentrations were calculated between the birth year and the ESCAPE monitoring years. The measurements from LUR models were then estimated for the birth year based on the temporal trend. The procedure assumed a constant spatial pattern of air pollution over time. The monitoring sites were located over each region to capture the spatial variation of air pollution at the residential address for each participant. The data quality was examined and assured, e.g. only sites with high-quality data for at least 75% of the days in a year were used.

Additionally, for each study area, data on 7-day moving average concentrations of NO_2 and PM_{10} preceding spirometric measurements were collected from a local monitoring station to control for the confounding effects of short-term air pollution exposure. The stations were 9 km and 2 km away from the centres of Munich and Wesel, respectively.

2.4. Statistical analyses

Longitudinal analyses were performed using multivariable linear mixed effects models with random subject intercepts, separately for Munich and Wesel. Region-specific effect estimates were then pooled using meta-analysis. In each model, an interaction term between the air pollutant and age was used to quantify linear change in FEV_1 or FVC from ages 6 to 15 in association with exposure to the air pollutant during the first year of life. Thus, the effect estimates were presented as the annual changes in z-scores of FEV_1 or FVC from ages 6 to 15 per unit increase in air pollutants. In this study, the mean of region-specific IQRs of air pollutants were used as the unit to describe the effect estimations.

The main models were additionally adjusted for a set of priori-selected covariates considering their potential confounding effects (Gehring et al., 2013; Milanzi et al., 2018): log-transformed weight, maternal smoking during pregnancy, maternal age at delivery, maternal and paternal atopy, maximal parental education, breastfeeding ≥12 weeks, passive smoking/natural gas cooking/mould/furry pets in home during the first year, respiratory infections in the past 4 weeks. The maximal parental education was defined as a categorical variable according to the highest number of years of education reported by either parent (low: <10 years, medium: =10 years or high: >10 years).

Stratified analyses were performed by maternal age (20–28, 29–34 and ≥35 years), asthmatic status, and breastfeeding ≥12 weeks, to explore their potential modifying effects. To respect the temporality between exposure and outcome, asthma manifesting before age 6 should be applied for in the stratified analyses. However, the small sample size of diagnosed cases (n = 36 in Wesel and n = 11 in Munich) precluded the reliable analysis. As with previous birth cohort study (Milanzi et al. 2018), we used the asthmatic status between the ages 3–15 years as a compromised indicator under the assumption that children who would develop asthma in later life had similar susceptibility or pre-asthmatic conditions in the very early period. Asthma was defined according to Global Allergy and Asthma European Network (GA^2LEN) (Carlsen et al., 2006; Håland et al., 2006). Briefly, asthma was reported if there were at least two positive answers to the three questions during each follow-up: (1) 'Has a doctor ever diagnosed asthma in your child?'. (2) 'Has your child had wheezing or whistling in the chest in the past 12 months?'. (3) 'Has your child been prescribed asthma medication in the past 12 months?' Data from Munich were not analysed directly in the stratified analyses due to limited cases, e.g. only 23 children developed asthma between ages 3–15. In Wesel, the medium sample sizes of some subgroups might have also reduced the power of significant tests (e.g. 91 children with asthma between ages 3 and 15). We therefore repeated stratified analyses after pooling data from Munich and Wesel together, assuming that participants in both areas were homogeneous.

2.5. Sensitivity analyses

Several sensitivity analyses were performed to check the robustness of our main findings. First, extended models were performed by additionally controlling for log-transformed birth weight, older siblings, cohort, childcare attendance and wheezing in the past 12 months. Second, we repeated the main analyses by only including children with complete three measurements at ages 6, 10 and 15, and by only using data at ages 10 and 15. In addition, we repeated the main models with additionally adjustment for respective short-term air pollutants: the long-term NO_2 models were adjusted for short-term NO_2. The long-term PM models were all adjusted for short-term PM_{10} due to the lack of short-term data on other PM-fractions. This strategy could be justified by the high correlations between different PM components (Gehring et al. 2013). Finally, we compared the effect estimates of infancy exposure between participants moved or not after the age of 1. All sensitivity analyses were confined to children in Wesel considering spirometric measurements for children in Munich were only performed at ages 6 and 15, and the lack of data on 7-day moving average of PM_{10} in Munich at age 6.

Subgroup differences in effects of air pollution were examined using meta-regression. For example, the difference in impacts of NO_2 on FEV_1 between Munich and Wesel was tested by setting the region-specific coefficients as the dependent variable (weighted by the variances), and a binary variable representing regions as the predictor.

R software (version 3.6.1) was used for analyses. Linear mixed effects models were fitted using the *lmer()* function from the "lme4" package (Bates et al. 2015). Meta-regressions were performed using the *mvmeta() function* from the "mvmeta" package (Gasparrini and Gasparrini 2019). P-values < 0.05 were considered statistically significant.

3. Results

3.1. Characteristics of study population

Nearly 60% of participants had parents with high educational level, particularly for those in Munich (Table 1). In addition, 41% and 34% of children had an atopic mother or father. Of the participants, over one-sixth were born from mothers aged ≥35 at delivery, 60% were breastfed for at least 12 weeks, and 12% developed asthma between ages 3 and 15. Table 2 summarizes the results of spirometric measurements from age 6 to age 15.

Table 1
Summary of population characteristics. Data are presented as number (%).

	Total	Munich	Wesel
Subjects	915 (100.0)	181 (19.8)	734 (80.2)
Subjects from GINIplus cohort	820 (89.6)	181 (100.0)	639 (87.1)
Birth weight (g)[a]	3520 (3200–3840)	3410 (3150–3711)	3550 (3200–3870)
Weight (kg)[a]			
6-year follow-up	22.8 (20.8–25.0)	22.0 (20.0–23.8)	23.2 (21.0–25.6)
10-year follow-up	36.6 (32.8–42.4)	32.1 (31.1–38.0)	36.7 (32.8–42.4)
15-year follow-up	62.0 (55.0–69.0)	60.0 (54.0–66.0)	62.0 (55.8–69.0)
Asthma between 3 and 15 years	114 (12.5)	23 (12.7)	91 (12.4)
Breastfeeding ≥12 weeks	533 (58.3)	130 (71.8)	403 (54.9)
Maternal age (year)			
≤28	215 (23.5)	29 (16.0)	186 (25.3)
29–34	543 (59.3)	106 (58.6)	437 (59.5)
≥35	157 (17.2)	46 (25.4)	111 (15.1)
Older siblings	465 (50.8)	76 (42.0)	389 (53.0)
Parental atopy			
Mother	373 (40.8)	106 (58.6)	267 (36.4)
Father	314 (34.3)	94 (51.9)	220 (30.0)
Maximal parental education			
Low (<10 years)	66 (7.2)	7 (3.9)	59 (8.0)
Medium (=10 years)	311 (34.0)	29 (16.0)	282 (38.4)
High (>10 years)	535 (58.5)	145 (80.1)	390 (53.1)
Smoking			
Mother during pregnancy	123 (13.4)	20 (11.0)	103 (14.0)
Anyone in 1st-year life	222 (24.3)	22 (12.2)	200 (27.2)
Gas for cooking in 1st-year life	45 (4.9)	13 (7.2)	32 (4.4)
Mold/dampness in 1st-year life	211 (23.1)	64 (35.4)	147 (20.0)
Furry pets in 1st-year life	132 (14.4)	22 (12.2)	110 (15.0)
Childcare attendance at the 2nd year	34 (3.7)	21 (11.6)	13 (1.8)
Movers	476 (52.0)	125 (69.1)	351 (47.8)
Cold or respiratory infections in past 4 weeks			
6-year follow-up	302 (33.0)	67 (37.0)	235 (32.0)
10-year follow-up	236 (25.8)	55 (30.4)	181 (24.7)
15-year follow-up	233 (25.5)	54 (29.8)	179 (24.4)

[a] Median value (the interquartile range).

3.2. Air pollution exposure during infancy and annual change in lung function

The median concentrations of most air pollutants were slightly higher in Wesel than in Munich (Table 3). Exposure during the first year of life was associated with reduced lung function development for all air pollutants (Table 4). Annual reduction of FEV_1 z-scores ranged from −0.012 [95% confidence interval (CI): −0.014, −0.009] per IQR increase in $PM_{2.5}$ to −0.023 (95%CI: −0.028, −0.018) per IQR increase in PM_{coarse}. Annual decline in FVC z-scores ranged from −0.006 (95%CI: −0.008, −0.003) to −0.011 (95%CI: −0.019, −0.003) per IQR increase in air pollutants. There was no significant difference in effect estimates for children in Munich and Wesel (P-values > 0.05). However, the point effect estimate of NO_2 in Wesel was twice as high as that in Munich. Region-specific analyses indicated that in Munich the adverse effects of infancy exposure were only significant for FEV_1. In Wesel, the effect estimates of infancy exposure were higher on FEV_1 than on FVC.

3.3. Modifying effects of maternal age, breastfeeding and asthmatic status

There was no substantial difference for the effects of air pollution exposure during infancy on FEV_1 development for children born to mothers of different ages at delivery (Fig. 2). The effect estimates of $PM_{2.5}$, PM_{10} and PM_{coarse} on FVC were only significant for older mothers. Despite non-significant 95%CIs, the effect-point estimates of NO_2 and $PM_{2.5}$ absorbance for children born from mothers aged ≥35 years at delivery were twice as high than for those born from the mothers aged 20–28 years. Similarly, the effect estimates of infancy exposure were not significantly higher for children who developed asthma in later life compared with those without asthma (Fig. 3). For children breastfed for shorter than 12 weeks, reduced increase in FEV_1 associated with infancy exposure to NO_2 and $PM_{2.5}$ absorbance were significantly higher than their counterparts (Fig. 4). After pooling participants from Munich and Wesel, the inter-group differences in the effects of infancy exposure became statistically significant for certain air pollutants (see Supplemental Figures S1-S3). For example, the z-score of FVC associated with infancy exposure to NO_2 declined annually by −0.026 (95%CI: −0.040, −0.011) for children with asthma and −0.006 (95%CI: −0.013, 0.000) for those without asthma (P-value of difference = 0.02).

3.4. Sensitivity analysis

Results of the sensitivity analyses indicated that the main findings were robust to controlling for additional potential confounders or the use of only complete cases (see Supplemental Tables S1-S3). Effect

Table 2
Summary of spirometric measurements at each time point of follow-up for different population subgroups.

	Munich (n = 181)				Wesel (n = 734)			
	Subjects	6th-year	10th-year	15th-year	Subjects	6th-year	10th-year	15th-year
FEV_1								
T3	172	0.13 ± 1.10	0.82 ± 1.18	0.16 ± 1.16	734	0.11 ± 1.15	0.37 ± 0.95	−0.14 ± 1.12
T2	4[a]	–	–	–	540	–	0.37 ± 0.95	−0.08 ± 1.10
T3C	2[b]	–	–	–	206	0.17 ± 1.11	0.33 ± 0.92	−0.10 ± 1.05
FVC								
T3	130	−0.85 ± 1.05	0.13 ± 1.06	0.15 ± 1.08	619	−0.14 ± 1.12	−0.31 ± 0.97	−0.06 ± 1.08
T2	4[a]	–	–	–	487	–	−0.32 ± 0.97	−0.02 ± 1.07
T3C	2[b]	–	–	–	120	−0.63 ± 1.61	−0.21 ± 0.96	0.02 ± 1.04

T3: subjects with spirometric data for at least two time points of follow-up.
T2: subjects with spirometric data at 10-year and 15-year follow-ups.
T3C: subjects with spirometric data at all 6-year, 10-year and 15-year follow-ups.
The T3 subgroup, i.e. the full data set, was used for the main analyses. The T2 and T3C subgroups were used in the sensitivity analyses to test the robustness of the main analyses.
[a] Only four subjects in Munich had spirometric data at 10-year and 15-year follow-ups, who were then excluded from the summary due to the small count.
[b] Only two subjects in Munich had spirometric data at all 6-year, 10-year and 15-year follow-ups, who were then excluded from the summary due to the small count.

Table 3
Summary of estimated annual concentrations of air pollution at residential addresses during the first year of life.

	Munich (n = 181)		Wesel (n = 734)		IQR_avr[a]
	Min-max	Median (25th-75th)	Min-max	Median (25th-75th)	
NO_2 (μg/m^3)	11.6–43.1	20.2 (17.3–24.8)	19.7–62.8	23.2 (22.0–25.1)	5.3
$PM_{2.5}$ absorbance (10^{-5}/m)	1.3–2.4	1.7 (1.6–1.8)	1.0–3.1	1.2 (1.1–1.3)	0.2
$PM_{2.5}$ (μg/m^3)	11.4–15.9	13.3 (12.7–14.1)	15.8–21.4	17.2 (17.0–17.8)	1.1
PM_{10} (μg/m^3)	14.8–26.0	20.5 (19.0–21.8)	23.9–31.6	25.2 (24.5–26.1)	2.2
PM_{coarse} (μg/m^3)	4.1–11.3	6.3 (5.7–7.5)	1.9–13.8	8.4 (8.1–8.7)	1.2

[a] IQR_avr refers to the mean value of interquartile ranges of air pollution concentrations in Munich and Wesel for each pollutant. It works as the unified unit to describe the adverse effects of air pollution exposure.

Table 4
Annual change in lung function (z-scores with 95% confidence intervals) for children in Munich and Wesel from ages 6 to 15 per interquartile range increase in air pollutants during the first year of life.

	FEV_1			FVC		
	Overall	Munich	Wesel	Overall	Munich	Wesel
NO_2 (μg/m^3)	−0.021 (−0.036, −0.007)	−0.012 (−0.027, 0.003)	−0.027 (−0.035, −0.020)	−0.011 (−0.019, −0.003)	−0.006 (−0.023, 0.012)	−0.012 (−0.021, −0.003)
$PM_{2.5}$ absorbance (10^{-5}/m)	−0.020 (−0.025, −0.015)	−0.017 (−0.029, −0.006)	−0.021 (−0.027, −0.015)	−0.009 (−0.015, −0.003)	−0.007 (−0.020, 0.005)	−0.010 (−0.016, −0.003)
$PM_{2.5}$ (μg/m^3)	−0.012 (−0.014, −0.009)	−0.013 (−0.022, −0.005)	−0.012 (−0.014, −0.009)	−0.006 (−0.008, −0.003)	−0.008 (−0.017, 0.001)	−0.005 (−0.008, −0.002)
PM_{10} (μg/m^3)	−0.016 (−0.019, −0.012)	−0.017 (−0.027, −0.007)	−0.015 (−0.019, −0.012)	−0.007 (−0.011, −0.004)	−0.007 (−0.018, 0.004)	−0.007 (−0.011, −0.003)
PM_{coarse} (μg/m^3)	−0.023 (−0.028, −0.018)	−0.018 (−0.031, −0.005)	−0.024 (−0.030, −0.019)	−0.011 (−0.017, −0.005)	−0.009 (−0.024, 0.006)	−0.011 (−0.017, −0.005)

FEV_1: forced expiratory volume in one second; FVC: forced vital capacity. Z-scores were calculated according to lung function normal values for kids in Germany. Linear mixed effects models were applied.
Significant tests were performed to test the effect estimates of air pollution between Munich and Wesel for FEV_1 and FVC separately, with no substantial difference detected (all P-values > 0.05).

estimates of infancy exposure were similar between participants moved or not after the age of 1 but tended to be slightly weaker in movers (see Supplemental Figures S4).

4. Discussion

In the present study, we explored the adverse effects of air pollution exposure in the first year of life on the longitudinal change of lung function in children in Munich and Wesel, Germany. We found reduced development of lung function in children from ages 6 to 15 following increased air pollution exposure during infancy in both regions, with FEV_1 potentially more affected than FVC. The impacts of infancy exposure on lung function were higher for children born from older mothers, breastfed for less than 12 weeks, and those who developed asthma between 3 and 15 years for certain air pollutants.

Previously, some studies have assessed the longitudinal effects of air pollution exposure on lung function development in children. He and colleagues found substantial deficits in lung function growth among schoolchildren aged 9.9 ± 1.2 years within 6 months of follow-up, such that FEV_1 growth was declined at a speed of −63 ml/year for boys in the highly-polluted district of Guangzhou, China (He et al. 2010). Gauderman et al. reported significant impacts of exposure to present air pollutants on the growth of FEV_1, FVC and maximal mid-expiratory flow rate for children from ages 10 to 18 years in the USA (Gauderman et al. 2004). For example, the growth of FEV_1 and FVC was reduced by −101.4 ml and −95.0 ml per 34.6 ppb increase in NO_2 over the 8-year period. In Mexico City, air pollution exposure in the preceding six months was associated with reduced growth of FEV_1 and FVC for children aged 8 during the next 3-year follow-up (Rojas-Martinez et al. 2007). These findings indicate that air pollution exposure is negatively associated with lung function growth during early adolescence. However, most of these longitudinal studies have focused on air pollution exposure during middle or later childhood, and the impacts of exposure during infancy remains largely unclear.

To the best of our knowledge, this is one of the few studies that explore the association between infancy exposure to air pollution and the change in lung function development until adolescence. Our findings of reduced growth of lung function from ages 6 to 15 were consistent with results from the Dutch population-based PIAMA birth cohort study (Milanzi et al. 2018). In the Netherlands, for per IQR increase in air pollutants during 0–4 years, the growth of FEV_1 in children was reduced by −0.17% to −0.33% annually from ages 8 to 16. By contrast, the Swedish BAMSE study reported non-significant change in lung function growth from ages 8 to 16 after air pollution exposure in the first year of life (Schultz et al. 2016). The UK ALSPAC cohort study found that exposure to higher PM_{10} within the first year of life was associated with lower lung function at age 8 (Cai et al. 2020). However, this study did not observe significant associations between early air pollution exposure with reduced lung function at age 15 or impaired lung function development from ages 8 to 15. Our study, therefore, adds to the evidence base for adverse effects of early air pollution exposure on the lung development in children.

It is beyond the scope of this study to clarify the mechanisms that may underlie the adverse effect of air pollution on lung function development due to the lack of more information on the cellular and molecular levels. However, some previous studies have indicated that this harmful development may be due to airway inflammation and oxidative damage in the lung, which are induced directly by high-oxidative pollutants such as NO_2 or indirectly by PM via epigenetic changes (Gruzieva et al., 2017; Perez et al., 2010). These pathophysiologic changes may trigger the small airway remodelling and other histological abnormalities of the lung tissue (Churg et al. 2003). Compared with adolescents and adults, infants are particularly vulnerable to air pollutants because of their higher oxygen consumption, smaller lung surface area per unit weight, more permeable airway epithelium, narrower airways, and premature defence of the lung (Salvi, 2007; WHO,

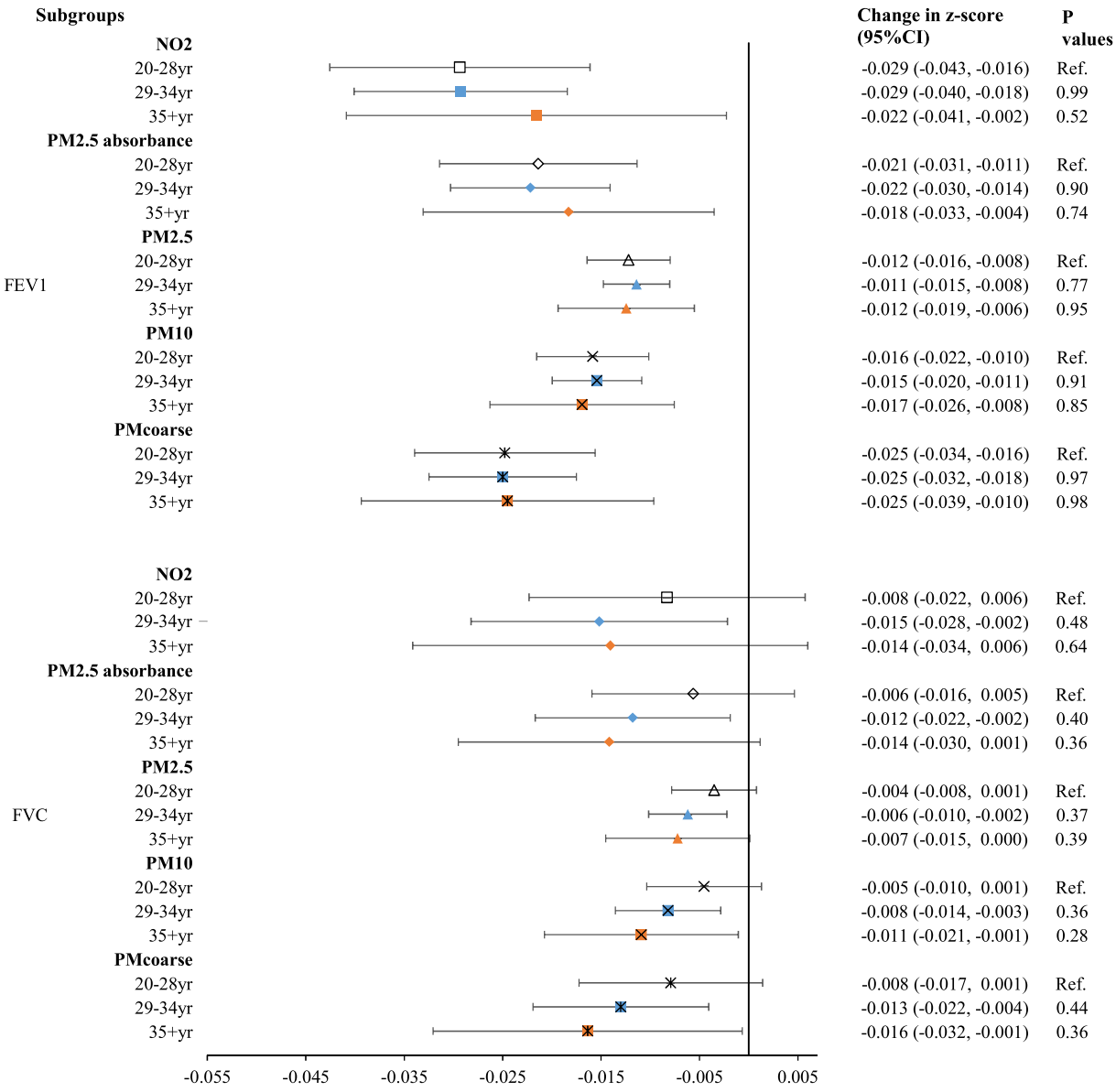

Fig. 2. Annual change in lung function (z-scores with 95% confidence intervals) from ages 6 to 15 per interquartile range increase in air pollutants during the first year of life stratified by maternal age at delivery in Wesel. Significant tests were performed using meta-regression, with children born from mother aged 20–28 years set as the references.

2018). Several studies have suggested that respiratory impairment during the critical early period may influence the pulmonary function development for a long period (Bonnet et al., 2005; Zhang et al., 2019).

In this study, we found that there was no significant difference in the effect estimates for air pollution exposure in Munich and Wesel. However, the point effect estimate of NO_2 in Wesel was twice as high as that in Munich. Based on the data available, it is difficult to explain why this regional difference was only obvious for the effect estimate of NO_2. The air pollution concentrations in Wesel were slightly higher than in Munich. However, only the concentrations of NO_2 in both regions were lower than the WHO air quality standards (WHO 2006). It is speculated that the varied effect estimates of NO_2 in the two regions may be relevant to the low-to-moderate exposure levels. Previously, the Swiss BILD birth cohort study explored the adverse effect of long-term air pollution exposure below WHO-limits on children's lung function impairment. It was reported that the reduction in lung function per unit increase in NO_2 concentration since birth was more pronounced for individuals with moderate exposure than children with low exposure. However, further studies are required to justify this speculation and explore whether it may also hold for other air pollutants in a low-to-moderate exposure scenario.

A series of spirometric indices has been developed to measure different aspects of the lung function. Given the various units and value ranges, few studies have examined whether there is a substantial difference in the adverse effects of air pollution across different spirometric indices. Our study tried to address this research gap by using the standardised z-scores. Our finding of higher effects on FEV_1 than on FVC indicates that early-life air pollution exposure is more likely to limit airway size than to restrict the lung volume. The result is partly consistent with the PIAMA birth cohort study, which reported negative effects of air pollution on the growth of FEV_1 but non-significant effects on FVC (Milanzi et al. 2018).

The negative impacts of air pollution exposure on lung function may not be equal in all children with some subgroups being potentially more vulnerable. Few studies have reported a higher vulnerability amongst children with asthma (Gehring et al., 2013; Rojas-Martinez et al., 2007). However, the majority of studies shows no modifying effect of asthmatic status on the association between air pollution exposure and lung

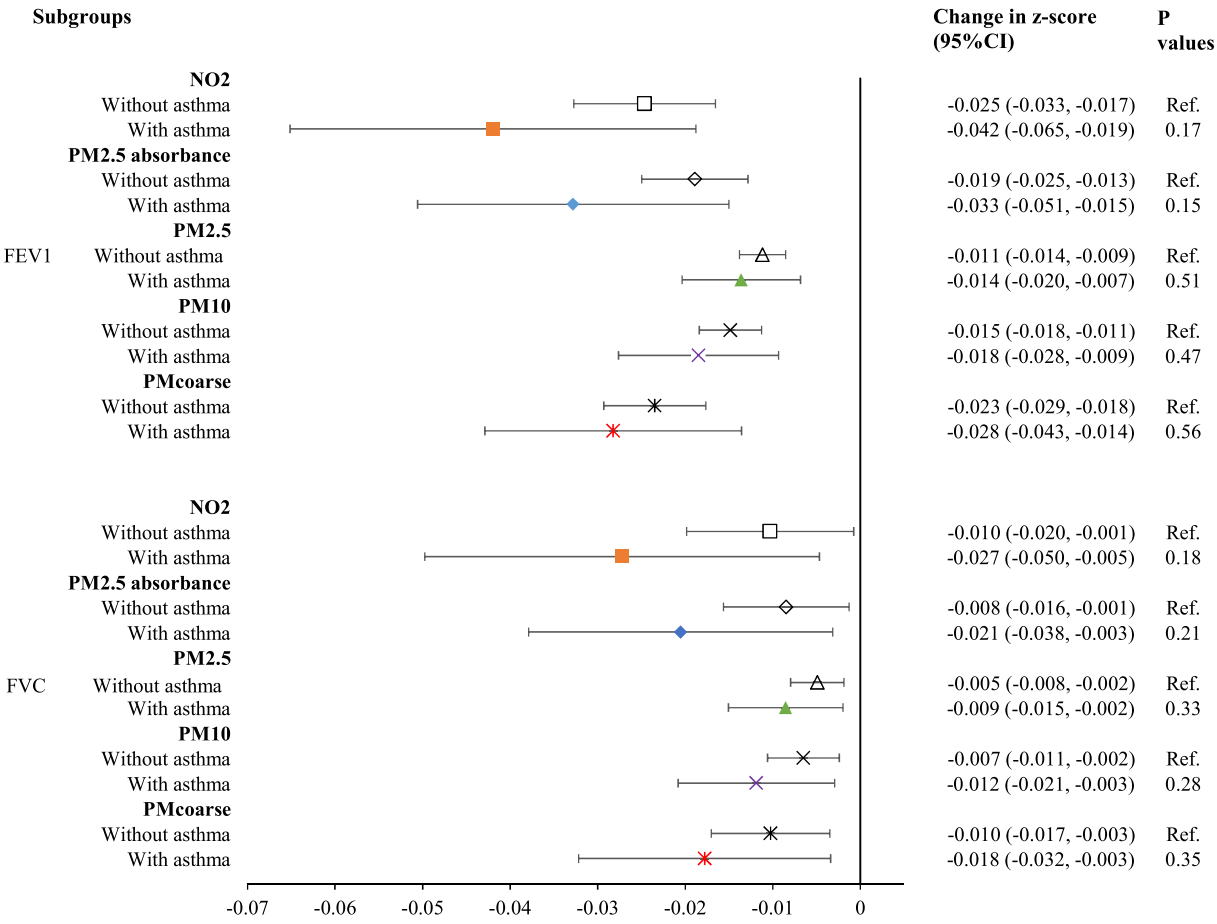

Fig. 3. Annual change in lung function (z-scores with 95% confidence intervals) from ages 6 to 15 per interquartile range increase in air pollutants during the first year of life stratified by asthma in Wesel. Significant tests were performed using meta-regression, with children without asthma set as the references.

function (Gauderman et al., 2004; Schultz et al., 2017). Similarly, we did not observe substantial difference in the effect estimates of air pollution for children with and without asthma while the point effect estimates were higher for asthmatic children than their healthy counterparts. These non-significant findings might be due to the small sample sizes of these studies. For example, only 12% of children (91 cases) developed asthma between the ages of 3–15 in Wesel. To improve the power of our analyses, we pooled samples from Munich and Wesel, assuming characteristics of children in both areas were homogeneous. The pooled analysis showed that the effect estimates of some air pollutants were significantly higher for asthmatic children than for non-asthmatic children. This finding partly justifies the aforementioned speculation and suggests that the modifying effect of asthma, if it exists, points towards increasing the vulnerability for children with asthma (Fuertes et al. 2015). Although mechanisms of the modifying effect of asthma remain largely unclear, some studies suggest that individuals with greater airway liability may be more susceptible to air pollution (Boezen et al., 1998; Tang et al., 2007). In our case, asthma measured later in childhood would be a proxy for the pre-asthmatic condition that might have already been present in the first year of life. Without necessary data in our cohorts, we could not testify this speculation. However, this research question warrants exploration by further studies.

Older maternal age at delivery is a confirmed risk factor for a variety of health outcomes in offspring, e.g. autism and Trisomy 21, while little information is available for lung function (Bleyer, 1938; Sandin et al., 2012). A study that investigated 10,692 adults from 13 countries reported that older maternal age was associated with higher lung function status in adulthood (Real et al. 2018). Another study found that lung function decline accelerated in adults born from mothers older than 31 years old in two European cohorts (Dratva et al. 2016). Despite different research questions and conclusions, the two studies provided some research clues regarding the influence of maternal age on the lung function development in offspring. In comparison, we found that children born from mothers 35 years old or older had reduction in FVC growth until adolescence after exposure to air pollution during infancy. Our finding might be relevant for the development of health promotion strategies in this air-polluted world where maternal age is increasing substantially.

Abundant evidence shows that breastfeeding may have protective effects on pediatric health (e.g. lung function and cardiovascular conditions), and mitigate the adverse effects of environmental hazards (Dong et al., 2013; Waidyatillake et al., 2013). However, only one cross-sectional study has explored the interactive effect of breastfeeding and air pollution exposure on lung function of children: In China, lung function FEV_1 and FVC in 339 schoolchildren aged 11.6 ± 2.1 years was negatively associated with air pollution exposure during the previous three years, with those breastfed for less than three months more vulnerable (Zhang et al. 2019). Our study goes a step further by assessing the modifying effect of breastfeeding on the longitudinal change in lung function development associated with exposure to air pollution during the first year of life. We found that the effect estimates of some air pollutants were significantly higher for children with breastfeeding less than 12 weeks than those with more breastfeeding. It is speculated that the immune factors and other cytokines in breast milk may play protective roles in the pathways of oxidative stress and systematic proinflammatory responses caused by air pollution exposure.

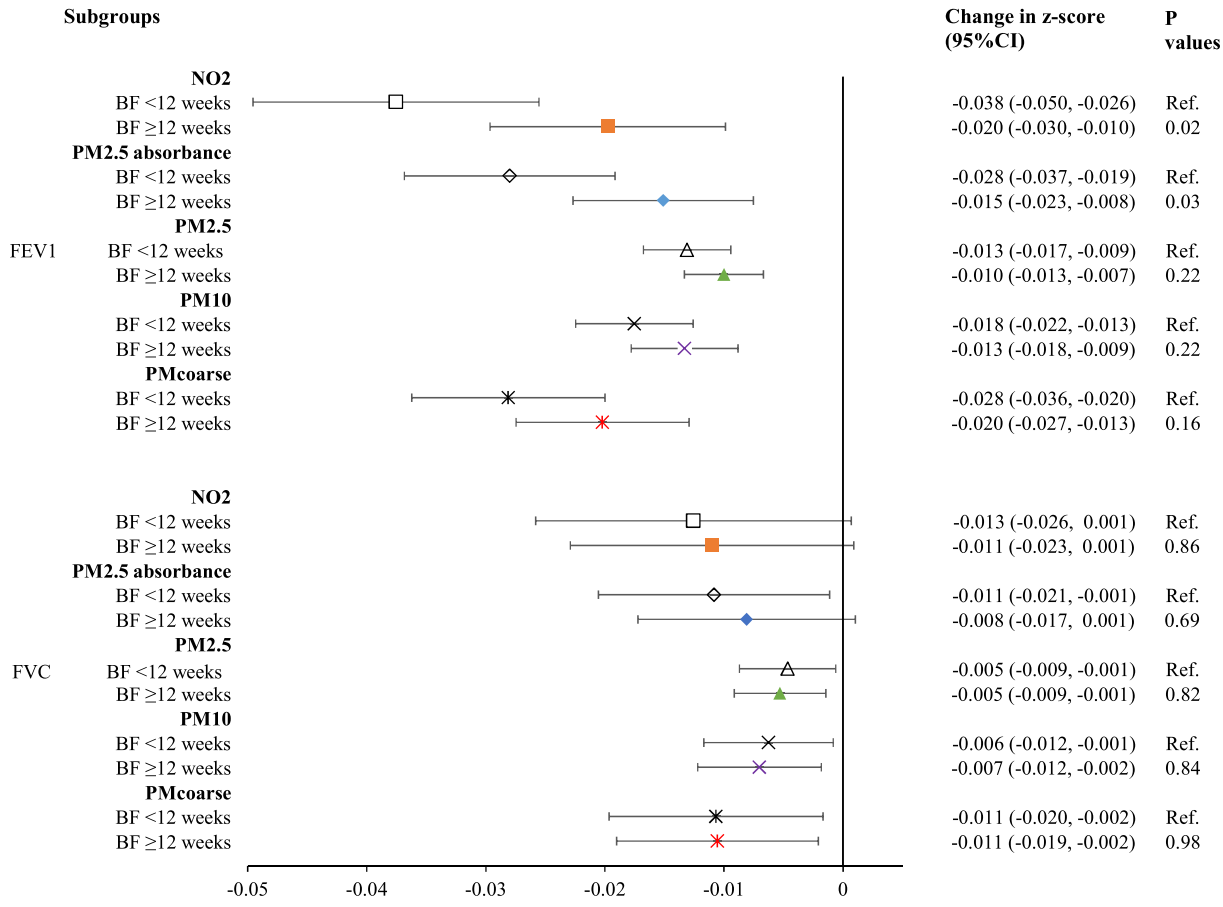

Fig. 4. Annual change in lung function (z-scores with 95% confidence intervals) from ages 6 to 15 per interquartile range increase in air pollutants during the first year of life stratified by duration of breastfeeding (BF) in Wesel. Significant tests were performed using meta-regression, with children breastfed <12 weeks set as the references.

5. Strengths & limitations

Our study has several strengths. First, we explored the impacts of air pollution exposure during infancy on the change of lung function until adolescence using the two largest birth cohorts in Germany. Second, we applied spirometric measurements across three time points, i.e. ages 6, 10 and 15, which strengthened the reliability of our findings. Third, to our best knowledge, this is one of the first longitudinal studies to explore the potential modifying effects of older maternal age at delivery, and breastfeeding on lung function development after exposure to air pollution during infancy. Our findings help to identify risky and protective modifiers of environmental hazards in the early development of diseases.

Our study also has several limitations that need to be acknowledged. Exposure data during the first year of life (1995–1999) were back-extrapolated using LUR models based on the measured data between 2008 and 2009, assuming a constant spatial pattern of air pollutants over time. This might introduce measurement bias. However, the robustness of this approach has been demonstrated by several cohort studies (Beelen et al., 2013; Milanzi et al., 2018). Due to the lack of data, we did not adjust for air pollution exposure after the age of 1 in the models. As a result, our findings may be partly associated with the cumulative exposure during the first six years. However, the small difference in the effect estimates between movers and non-movers indicated that our findings should not be biased substantially by exposures after the age of 1. Finally, the limited sample sizes of subgroups might have reduced the power of significant tests in stratified analyses. Although the extended analyses using pooled samples from Munich and Wesel have distinguished some inter-group differences, the modifying effects of advanced maternal age, asthmatic status of children and breastfeeding less than 12 weeks should be interpreted with caution.

6. Conclusions

Exposure to higher levels of air pollutants in infancy may impact lung function development in children up to adolescence, which seems to be more pronounced for airway size limitation than lung volume restriction. Higher maternal age at delivery, asthmatic status of children and breastfeeding for less than 12 weeks may increase the impacts of air pollution but their modifying effects warrant further exploration.

CRediT authorship contribution statement

Qi Zhao: Conceptualization, Formal analysis, Methodology, Software, Visualization, Writing - original draft, Writing - original draft, Writing - review & editing. **Sara Kress:** Validation, Writing - review & editing. **Iana Markevych:** Data curation, Writing - review & editing. **Dietrich Berdel:** Investigation, Project administration, Writing - review & editing. **Andrea von Berg:** Investigation, Project administration, Writing - review & editing. **Monika Gappa:** Investigation, Writing - review & editing. **Sibylle Koletzko:** Investigation, Writing - review & editing. **Carl-Peter Bauer:** Investigation, Investigation, Writing - review & editing. **Holger Schulz:** Data curation, Writing - review & editing. **Marie Standl:** Data curation, Investigation, Writing - review & editing. **Joachim Heinrich:** Data curation, Investigation, Writing - review & editing. **Tamara Schikowski:** Conceptualization, Methodology, Supervision, Validation, 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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Data sharing statement

Requests for additional data should be addressed to the corresponding author.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2020.106195.

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