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Genetic susceptibility to asthma increases the vulnerability to indoor air pollution

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Our findings from a South African birth cohort study show an association of indoor air pollution with reduced lung function at 6 weeks and 1 year of age, with a higher susceptibility in children with a genetic predisposition for asthma http://bit.ly/2NpkGRr

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ABSTRACT

Introduction: Indoor air pollution and maternal smoking during pregnancy are associated with respiratory symptoms in infants, but little is known about the direct association with lung function or interactions with genetic risk factors. We examined associations of exposure to indoor particulate matter with a 50% cut-off aerodynamic diameter of 10 µm (PM_{10}) and maternal smoking with infant lung function and the role of gene–environment interactions.

Methods: Data from the Drakenstein Child Health Study, a South African birth cohort, were analysed (n=270). Lung function was measured at 6 weeks and 1 year of age, and lower respiratory tract infection episodes were documented. We measured pre- and postnatal PM_{10} exposures using devices placed in homes, and prenatal tobacco smoke exposure using maternal urine cotinine levels. Genetic risk scores determined from associations with childhood-onset asthma in the UK Biobank were used to investigate effect modifications.

Results: Pre- and postnatal exposure to PM_{10} as well as maternal smoking during pregnancy were associated with reduced lung function at 6 weeks and 1 year as well as with lower respiratory tract infection in the first year. Due to a significant interaction between the genetic risk score and prenatal exposure to PM_{10}, infants carrying more asthma-related risk alleles were more susceptible to PM_{10}-associated reduced lung function ($p_{interaction}$=0.007). This interaction was stronger in infants with Black African ancestry ($p_{interaction}$=0.001) and nonexistent in children with mixed ancestry ($p_{interaction}$=0.876).

Conclusions: PM_{10} and maternal smoking exposures were associated with reduced lung function, with a higher susceptibility for infants with an adverse genetic predisposition for asthma that also depended on the infant's ancestry.

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Introduction

Indoor air pollution and tobacco smoke exposure are important risk factors for child health, with infants being a highly susceptible subgroup [1]. According to the Global Burden of Disease, Injuries and Risk Factors Study 2015, air pollution is the biggest environmental cause of death worldwide, with indoor air pollution accounting for about 2.9 million deaths and 85.6 million disability-adjusted life-years in 2015 [2]. Indoor air pollution arises from domestic activities of cooking, heating and lighting, particularly in low- and middle-income countries (LMICs). Three billion people worldwide are exposed to toxic amounts of indoor air pollution every day because they use solid fuels, a term that includes biomass fuels (derived from plant sources) and coal for combustion [1].

Similarly, tobacco smoke exposure is a major risk for poor health. Despite worldwide initiatives to reduce tobacco smoking, it is estimated that up to 40% of children are still exposed to environmental tobacco smoke [3]. The incidence of smoking is increasing in LMICs, especially among women of childbearing age, which leads to high tobacco smoke exposure in children [4, 5].

Indoor air pollution and tobacco smoke have been strongly associated with the development of childhood respiratory illness, particularly with lower respiratory tract infection (LRTI) and wheezing [1, 6]. Lung development and maturation is incomplete at birth and continues during the first years of life, making the lungs particularly vulnerable to damage during this critical time of lung development.

Recently, we showed that prenatal rather than postnatal exposure to indoor air pollution and tobacco smoke was associated with LRTI and wheezing in infants from the Drakenstein Child Health Study (DCHS), a South African birth cohort study, which highlights the importance of the timing of exposure on child respiratory health [6]. The precise mechanisms are still largely unclear, but it is hypothesised that prenatal exposure might act directly on the developing fetus or induce a systemic immune or inflammatory response. This inflammatory response might subsequently lead to placental insufficiency and reduced supply of oxygen and nutrients to the fetus [7, 8].

Asthma is a spectrum of airways disease that is highly heritable and associated with environmental exposures, including air pollution and tobacco smoke [9, 10]. A recent genome-wide association study of data from the UK Biobank study (13 962 cases and 300 671 controls) showed that a large extent of the variance in the liability of paediatric asthma is explained by common genetic variants (onset at ages between 0 and 19 years; h^2=25.6%) with 123 independent single nucleotide polymorphisms (SNPs) being genome-wide significant [11]. In addition to the direct associations between air pollution or tobacco smoke and asthma, evidence from toxicological and gene–environment studies further suggests that the association is particularly pronounced in genetically predisposed individuals [12, 13]. However, if and how a genetic predisposition for asthma also affects early lung development and its susceptibility to environmental exposures remains unclear.

In this study we used data from children in the DCHS to investigate associations of pre- and postnatal exposure to indoor air pollution (particulate matter with a 50% cut-off aerodynamic diameter of 10 µm (PM_{10})) or maternal smoking during pregnancy with infant lung function at 6 weeks and 1 year of age and effect modifications by a genetic predisposition for asthma.

Methods

Study design and study population

The DCHS, a population-based birth cohort, has been described previously [14–16].

Infants enrolled in the DCHS were followed from birth until at least 1 year of age [14]. Mothers were enrolled prenatally in their second trimester and followed through pregnancy at two primary care clinics serving two distinct populations (predominantly Black African ancestry or predominantly mixed ancestry). Mother–child pairs were followed from birth. All births occurred at a single, central facility (Paarl Hospital, Paarl, South Africa). Infants attended scheduled study visits at 6, 10 and 14 weeks and 6, 9 and 12 months of age, with lung function assessed at 6 weeks and 1 year.

The sample included in the present study was composed of 270 children who had all measurements available, including lung function at 6 weeks and 1 year of age and genotyping data.

Lung function testing was undertaken at 6 weeks (5–11 weeks) of age corrected for prematurity (<37 weeks) and then at 1 year (11–13 months). All testing was done in unsedated, behaviourally assessed quiet sleep as previously described [15, 17, 18]. Infant lung function variables assessed were functional residual capacity (FRC) and tidal volume, as measures of early lung growth [15]. Study staff trained in the recognition of LRTI documented all episodes, either ambulatory or hospitalised. We defined LRTI using World Health Organization case definition criteria [6].

Pregnant women were enrolled at 20–28 weeks of gestation, and prenatal (within 4 weeks of enrolment) and postnatal (between 4 and 6 months of the infant's life) home visits were undertaken to assess the home environment and measure indoor air pollution. PM_{10} was measured using a personal air sampling pump (AirChek 52; SKC, Eighty Four, PA, USA), connected to a styrene filter cassette (37 mm cassette blank; SKC) with a gravimetrically pre-weighed filter (PVC filter 37 mm×5 µm with support pad; SKC) left in homes for 24 h [6, 16]. Filters were weighed post-sampling and analysed using National Institute for Occupational Safety and Health method 0600 to obtain an average concentration over 24 h [19]. These average concentrations over 24 h were used as exposures in the analyses. Exposure to maternal tobacco smoke was assessed by prenatal urine cotinine measures in mothers. Urine cotinine was measured using the IMMULITE 1000 Nicotine Metabolite Kit (Siemens Medical Solutions Diagnostics, Glyn Rhonwy, UK). This provides a quantitative test using a competitive chemiluminescent immunoassay, which contains solid-phase beads coated with polyclonal rabbit anticotinine antibody. Quantitative analyses were used to classify exposure as <10 ng·mL^{-1} (nonsmoker), 10–499 ng·mL^{-1} (passive smoker/exposed) or $\geqslant$500 ng·mL^{-1} (active smoker) [6].

Assessment of genotypes

Offspring samples were selected for genotyping analysis based on a number of criteria relevant to the DCHS as a whole, including (but not limited to) maternal psychosocial risk/stressors and/or availability of offspring lung function data. DNA was isolated from cord blood samples that were collected at the time of delivery [20]. Genome-wide genotyping was performed in the 270 newborns using the Illumina Infinium PsychArray (n=119) and the Illumina Infinium Global Screening Array (n=151) (Illumina, San Diego, CA, USA). After quality control, SNPs were imputed on the 1000 Genomes reference panel (Phase III) using the Michigan Imputation Server [21]. Imputed genotypes reaching $R^2 \geqslant 0.3$ in both arrays were used in analyses. Principal components were calculated in the whole study sample using PLINK version 1.90b4 64-bit (www.cog-genomics.org/plink/1.9[22]).

Statistical analysis

We investigated the association between pre- and postnatal exposure to PM_{10} and maternal smoking during pregnancy with lung function at 6 weeks and 1 year of age in adjusted linear models and with LRTI in adjusted logistic models. *A priori* selected covariates that could potentially act as confounders included sex, birthweight (kg), age for weight *z*-scores at birth based on the Fenton Growth Chart, maternal HIV status, ancestry of child, age and height at time of lung function measurement, and socioeconomic status quartile. Associations with PM_{10} were additionally adjusted for maternal smoking behaviour during pregnancy based on prenatal urine cotinine measures. In a sensitivity analysis, associations with lung function were further adjusted for LRTI in the first year. All associations including genotyping data were additionally adjusted for genotyping array (PsychArray or Global Screening Array) and for the first five principal components to correct for population stratification (supplementary figure S1).

To investigate the impact of genetic factors on the association between PM_{10} or maternal smoking during pregnancy with early lung growth, we summarised the genetic susceptibility to childhood-onset asthma in a genetic risk score (GRS) and estimated its interaction with PM_{10} or maternal smoking during pregnancy on newborn lung growth in a linear regression analysis. The GRS was based on summary statistics from a recent genome-wide association study (GWAS) of childhood-onset asthma in the UK Biobank (13 962 cases and 300 671 controls) [11] and was calculated using PRSice [23]. PRSice calculates the sum of alleles weighted by their effect sizes estimated from a GWAS of the phenotype of interest in an independent sample (here from [11]) using an approach called clumping and thresholding. Clumping was used to obtain SNPs in linkage equilibrium with $r^2<0.1$ within a 250 bp window, keeping the SNP with the lower p-value observed in the external dataset for the analysis (refer to supplementary tables S1 and S2 for a list of SNPs that were included in the construction of the GRS after clumping and thresholding; summary statistics are published under https://genepi.qimr.edu.au/staff/manuelF/gwas_results/main.html). Multiple scores were then created for containing SNPs selected according to the significance of their association with the phenotype. As proposed in [23], the GRS that predicts the specific lung function parameter best (highest R^2) was used for analysis (supplementary table S3). Since the distribution of GRSs strongly depends on ancestry [24], GRSs were calculated in ancestrally homogeneous subgroups (Black African *versus* mixed ancestry) adjusted for sex, genotyping array and the first five principal components. The resulting GRSs were standardised (*z*-scores) to control for ancestry-specific differences in distribution before the data from both ancestries were merged for the subsequent interaction analyses.

Results

Description of study participants

The characteristics of the study participants (n=270 infants) are described in table 1. Around half of the infants were female (45%) and the infants were almost equally distributed between two population groups

TABLE 1 Demographics of infants used for analysis (samples with genotype information) as well as of infants from the whole study population

	Analysis sample	Whole study population	p-value
Subjects	270	1143	
Female	122 (45.2)	554 (48.5)	0.3435
Age at 6 weeks investigation months	1.7±0.3	1.8±0.4	0.0004
Age at 1 year investigation months	12.4±0.8	12.5±1.0	0.1427
Black African ancestry	151 (55.9)	632 (55.3)	0.8918
Mixed ancestry	119 (44.1)	511 (44.7)	
Global Screening Array for genotyping	151 (55.9)		
PsychArray for genotyping	119 (44.1)		
Birthweight kg	3.1±0.5	3.0±0.6	0.0474
Age for weight *z*-scores at birth based on the Fenton Growth Chart	−0.6±1.0	−0.6±1.1	0.7524
Height at 6 weeks investigation cm	55.3±3.1	55.2±2.8	0.4764
Height at 1 year investigation cm	74.0±3.1	73.8±3.2	0.3425
Mother HIV positive	66 (24.4)	248 (21.7)	0.3708
Socioeconomic status high	67 (24.8)	283 (24.8)	0.9270
Socioeconomic status moderate to high	66 (24.4)	290 (25.4)	
Socioeconomic status low to moderate	75 (27.8)	296 (25.9)	
Socioeconomic status low	62 (23.0)	274 (24.0)	
Active smoking during pregnancy#	80 (29.6)	352 (30.8)	0.0089
Passive smoke exposure during pregnancy#	129 (47.8)	479 (41.9)	
No tobacco smoke exposure during pregnancy#	60 (22.2)	262 (22.9)	
Prenatal PM_{10} exposure¶ $\mu g \cdot m^{-3}$	25.4 (4.7)	24.1 (4.4)	0.6574
Postnatal PM_{10} exposure¶ $\mu g \cdot m^{-3}$	21.3 (3.7)	22.5 (4.1)	0.6570
FRC at 6 weeks mL	77.7±15.7	77.6±16.1	0.9344
Tidal volume at 6 weeks mL	202.4±43.7	197.7±43.2	0.2097
FRC at 1 year mL	34.9±6.3	34.8±6.4	0.9358
Tidal volume at 1 year mL	92.5±13.9	93.0±14.2	0.6666
LRTI in the first year	89 (33.0)	359 (31.4)	0.6627

Data are presented as n, n (%) or mean±SD. PM_{10}: particulate matter with a 50% cut-off aerodynamic diameter of 10 µm; FRC: functional residual capacity; LRTI: lower respiratory tract infection. #: based on the maximum maternal prenatal cotinine level (<10 $ng \cdot mL^{-1}$ (nonsmoker), 10–499 $ng \cdot mL^{-1}$ (passive smoker/exposed) or ⩾500 $ng \cdot mL^{-1}$ (active smoker)); ¶: mean difference between pre- and postnatal PM_{10} exposure was not significant (p=0.270; Welch two-sample t-test). p-values are given for the difference in study characteristics between our analysis sample and the whole study population (continuous variables tested with the two-sample t-test; categorical variables with two categories tested with Fisher's exact test and with more than two categories tested with the Chi-squared test).

(56% Black African and 44% mixed ancestry). A high percentage of mothers were infected with HIV (24%) and there were many active smokers among pregnant women, as well as high rates of passive smoke exposure, as determined by maternal cotinine measurements. Approximately one-third of the children had at least one LRTI in the first year of life.

Due to the skewed distribution of PM_{10} exposure levels (supplementary figure S2), exposure levels were log-transformed prior to analyses. Prenatal PM_{10} levels were slightly higher than postnatal PM_{10} levels (difference not significant).

The study characteristics of our study population (n=270 samples with genotype data) were very similar to the characteristics of the whole study population (n=1143) (table 1).

PM_{10} and maternal smoking are associated with reduced infant lung function and LRTI

Prenatal exposure to PM_{10} was associated with reduced FRC at the age of 1 year (β-estimate −9.0 (95% CI −17.2–−0.9) per increase of interquartile range (IQR)) and postnatal exposure to PM_{10} with reduced tidal volume at 1 year (β-estimate −2.9 (95% CI −5.4–−0.5) per increase of IQR) (table 2). Maternal smoking during pregnancy was associated with a −2.4 (95% CI −4.7–−0.1) mL lower tidal volume at the age of 6 weeks as well as with higher odds for LRTI in the first year of life (table 2). Associations with FRC and tidal volume were not confounded by LRTI (supplementary table S4).

TABLE 2 Association between particulate matter with a 50% cut-off aerodynamic diameter of 10 µm (PM_{10}) and maternal smoking exposure with lung function (functional residual capacity (FRC) and tidal volume) at the age of 6 weeks and 1 year

	β-estimate (95% CI)	p-value
Prenatal		
PM_{10}		
FRC (6 weeks)	−1.9 (−4.5–0.7)	0.160
Tidal volume (6 weeks)	−0.4 (−1.3–0.6)	0.419
FRC (1 year)	−9.0 (−17.2–−0.9)	0.032#
Tidal volume (1 year)	−0.2 (−2.8–2.3)	0.851
LRTI (in the first year)	0.0 (−0.3–0.4)	0.915
Maternal smoking		
FRC (6 weeks)	−3.7 (−10.0–2.6)	0.249
Tidal volume (6 weeks)	−2.4 (−4.7–−0.1)	0.043#
FRC (1 year)	−6.7 (−25.6–12.2)	0.487
Tidal volume (1 year)	−4.1 (−10.1–1.8)	0.176
LRTI (in the first year)	1.0 (0.2–1.8)	0.016#
Postnatal		
PM_{10}		
FRC (1 year)	−4.3 (−12.5–3.9)	0.304
Tidal volume (1 year)	−2.9 (−5.4–−0.5)	0.022#
LRTI (in the first year)	0.0 (−0.3–0.4)	0.799

Effect estimates (β-coefficients) for PM_{10} are presented per increase of interquartile range (log(PM_{10}+1)), resulting in 1.66 µg·m^{-3} for prenatal PM_{10} and 1.28 µg·m^{-3} for postnatal PM_{10} exposure. Effect estimates for maternal smoking are presented for active smokers with passive smoking and no tobacco smoke exposure as reference category. LRTI: lower respiratory tract infection. All associations were adjusted for sex, birthweight (kg), age for weight *z*-scores at birth based on the Fenton Growth Chart, maternal HIV status, ancestry of child, age and height at time of lung function measurement, and socioeconomic status quartile. Associations with PM_{10} were additionally adjusted for maternal smoking behaviour during pregnancy based on prenatal urine cotinine measures. #: p-values <0.05 considered statistically significant.

Infants with a genetic predisposition for asthma are more susceptible to prenatal PM_{10} exposure

Although the GRS was not directly associated with lung function at 6 weeks or 1 year of age (supplementary table S3 and S5), we found a significant gene–environment interaction between the GRS and prenatal PM_{10} on FRC at 6 weeks of age ($p_{interaction}$=0.007) (table 3). The direction of interaction was consistent for FRC and tidal volume at 6 weeks as well as 1 year of age, with infants with a higher GRS being more susceptible to prenatal PM_{10} exposure, which corresponds to carrying more asthma-related risk alleles (figure 1). No interactions were found for LRTI.

Genetic susceptibility to prenatal PM_{10} exposure depends on ancestry

The genetic susceptibility to PM_{10} strongly depended on the infant's ancestry. We found a strong gene–environment interaction with prenatal PM_{10} exposure in infants with Black African ancestry, which was significant for FRC and tidal volume at 6 weeks as well as for tidal volume at 1 year, whereas no interactions were found for infants with mixed ancestry (table 3 and figure 1).

Discussion

In this study of infants from a poor peri-urban community in South Africa, we showed that pre- and postnatal exposure to PM_{10} as well as maternal smoking during pregnancy were associated with reduced lung function at the age of 6 weeks and 1 year. Of note, these associations were altered by genetic risk factors and ancestry: infants with a genetic predisposition for asthma were more susceptible to the adverse effects of prenatal PM_{10} and this interaction also depended on the infants' ancestry, with infants of Black African ancestry being more vulnerable.

Longitudinal cohort studies have shown that lung function trajectories are set in early life with a developmental window of susceptibility, which can be disrupted by both infectious and environmental exposures [25–27]. The present study provided evidence that early exposures to PM_{10} and maternal smoking during pregnancy not only affect susceptibility to develop childhood LRTI or wheezing [6], but are also directly associated with infant lung function at the age of 6 weeks as well as at 1 year.

TABLE 3 Interaction between the genetic risk scores for asthma and particulate matter with a 50% cut-off aerodynamic diameter of 10 µm (PM_{10}) and maternal smoking exposure on lung function (functional residual capacity (FRC) and tidal volume) at the age of 6 weeks and 1 year

	All		Black African ancestry		Mixed ancestry	
	β-estimate (95% CI)	p-value	β-estimate (95% CI)	p-value	β-estimate (95% CI)	p-value
Prenatal						
PM_{10}						
FRC (6 weeks)	−3.5 (−6.0–−1.0)	0.007#	−5.5 (−8.6–−2.4)	0.001#	−0.4 (−5.0–4.3)	0.876
Tidal volume (6 weeks)	−0.4 (−1.4–0.5)	0.351	−1.5 (−2.7–−0.3)	0.019#	1.2 (−0.4–2.8)	0.131
FRC (1 year)	−4.0 (−12.0–4.0)	0.328	−6.4 (−16.7–3.9)	0.228	2.1 (−13.3–17.6)	0.789
Tidal volume (1 year)	−1.3 (−3.7–1.2)	0.310	−3.5 (−6.7–0.3)	0.038#	0.9 (−3.9–5.6)	0.721
LRTI (in the first year)	0.0 (−0.3–0.4)	0.933	0.3 (−0.2–0.8)	0.231	−0.3 (−1.0–0.3)	0.317
Maternal smoking						
FRC (6 weeks)	3.4 (−0.9–7.6)	0.120	6.2 (−1.0–13.3)	0.093	−0.1 (−6.2–6.0)	0.976
Tidal volume (6 weeks)	0.6 (−0.9–2.2)	0.415	0.9 (−1.7–3.5)	0.494	1.0 (−1.0–3.1)	0.334
FRC (1 year)	9.0 (−3.5–21.5)	0.159	9.3 (−10.5–29.2)	0.359	14.3 (−3.6–32.2)	0.123
Tidal volume (1 year)	2.5 (−1.3–6.3)	0.199	1.8 (−4.6–8.2)	0.586	5.5 (−0.4–11.4)	0.070
LRTI (in the first year)	−0.1 (−0.6–0.4)	0.705	−0.2 (−1.1–0.7)	0.671	0.6 (−0.3–1.5)	0.177
Postnatal						
PM_{10}						
FRC (1 year)	4.4 (−4.5–13.3)	0.336	3.1 (−11.1–17.3)	0.670	7.9 (−6.7–22.4)	0.294
Tidal volume (1 year)	−1.0 (−3.8–1.8)	0.491	1.7 (−6.4–3.0)	0.487	−1.4 (−6.7–3.8)	0.588
LRTI (in the first year)	0.0 (−0.4–0.4)	0.920	0.4 (−0.5–1.4)	0.376	−0.4 (1.2–0.4)	0.314

Effect estimates (β-coefficients), 95% confidence intervals and p-values are given for the interaction between PM_{10} or maternal smoking with the continuous genetic risk score (GRS) on lung function. PM_{10} is presented per increase of interquartile range (log(PM_{10}+1)), resulting in 1.66 µg·m^{-3} for prenatal PM_{10} and 1.28 µg·m^{-3} for postnatal PM_{10} exposure. Effect estimates for maternal smoking are presented for active smokers with passive smoking and no tobacco smoke exposure as reference category. LRTI: lower respiratory tract infection. GRS are given as *z*-scores. All associations were adjusted for sex, birthweight (kg), age for weight *z*-scores at birth based on the Fenton Growth Chart, maternal HIV status, ancestry of child, age and height at time of lung function measurement, socioeconomic status quartile, genotyping array, and the first five principal components to correct for population stratification (see supplementary figure S1). Associations with PM_{10} were additionally adjusted for maternal smoking behaviour during pregnancy based on prenatal urine cotinine measures. #: p-values <0.05 considered statistically significant.

Consequently, prenatal exposures to indoor PM_{10} and maternal smoking during pregnancy might be risk factors for reduced airflow and chronic obstructive pulmonary disease later in life [28, 29].

We recently reported in this cohort that the timing of exposure was crucial to the susceptibility to childhood LRTI or wheezing [6]; exposure during pregnancy was an even stronger risk factor for respiratory diseases in early life rather than postnatal exposure. This is consistent with data from the present study, in which we found stronger associations with prenatal exposures, especially in interaction with a genetic predisposition for asthma. In our study, not every infant exposed to high levels of prenatal PM_{10} had the same risk for reduced lung function: our gene–environment interaction analyses revealed that infants who carried more asthma-related risk alleles were more susceptible to PM_{10}-associated reduced lung function.

At present, little is known about the genetic susceptibility to environmental pollutants and their association with lung function, and most evidence is based on samples of European ancestry. Asthma is one of the few respiratory outcomes with robust evidence that associations with environmental exposures can be altered by genetic risk factors [12, 13]. This evidence is mainly based on a candidate SNP study of 5115 children [12] as well as a genome-wide interaction analysis (~1500 children in the discovery cohort and ~1800 children in the replication cohort) [13]. In addition, some studies have shown the relevance of gene–environment interactions with ambient air pollution, occupational exposures as well as smoking for adult lung function [30–32]. Our current study extends this evidence by showing the importance of gene–environment interactions for infant lung function in a non-European cohort.

Strengths and limitations

Strengths of this study include the longitudinal follow-up, prospective collection of data, high cohort retention, and repeated objective measures of indoor air pollution through the prenatal period and through infancy. A further strength was the carefully conducted lung function measurements, which were consistently assessed by the same investigators, using the same testing techniques. Lung function was

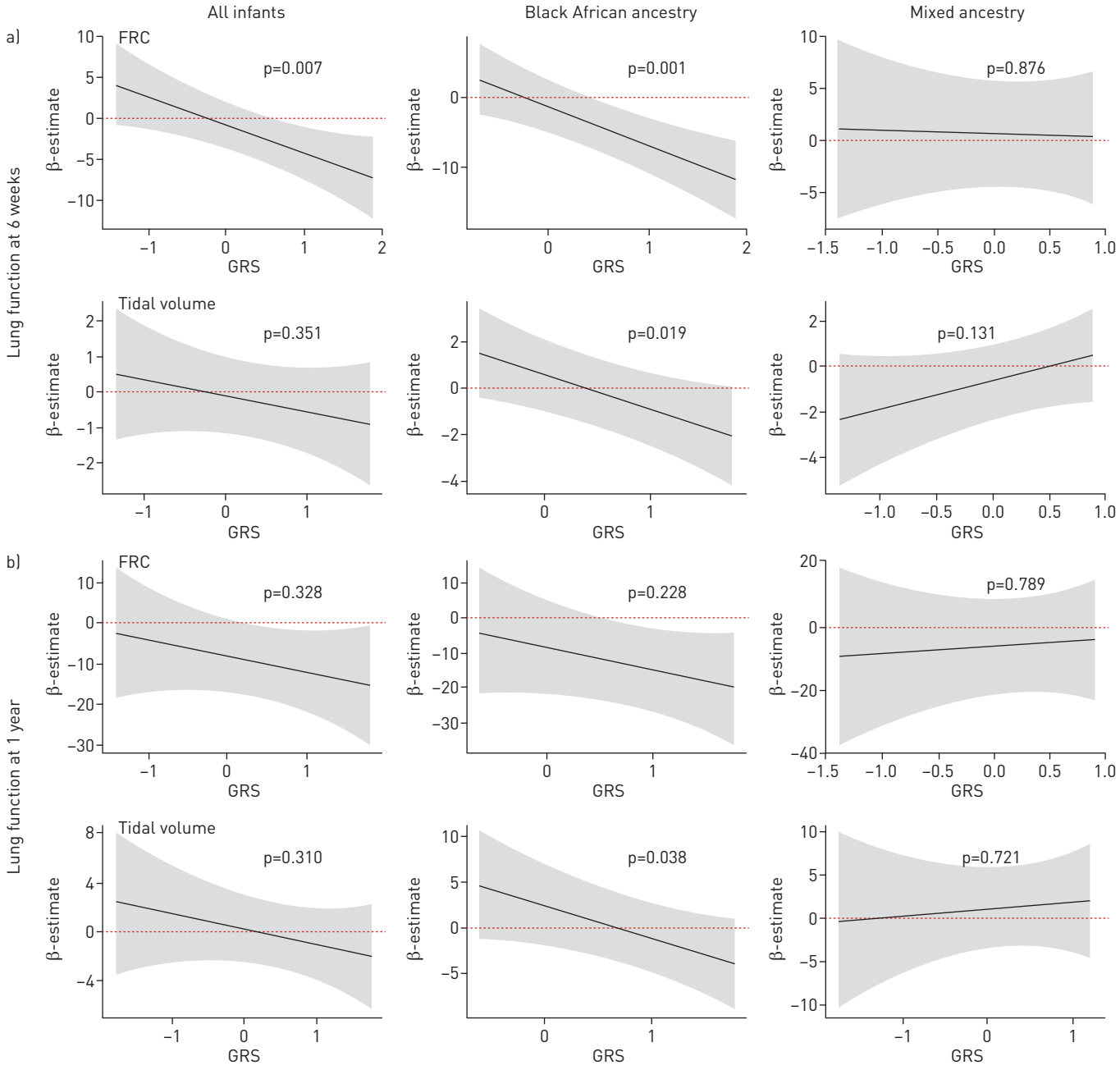

FIGURE 1 Interaction between genetic risk score (GRS) and prenatal exposure to particulate matter with a 50% cut-off aerodynamic diameter of 10 µm (PM_{10}) on lung function (functional residual capacity (FRC) and tidal volume) at the age of a) 6 weeks and b) 1 year. Associations between PM_{10} and lung function are shown in dependence of GRS levels. p-values are shown for the interaction terms. Effect estimates (β-coefficients) are presented per increase of 1.66 µg·m^{-3} in prenatal PM_{10} exposure (interquartile range (log(PM_{10}+1))). Shading indicates 95% confidence intervals. GRSs are given as *z*-scores. All associations were adjusted for sex, birthweight (kg), age for weight *z*-scores at birth based on the Fenton Growth Chart, maternal HIV status, ancestry of child, age and height at time of lung function measurement, socioeconomic status quartile, genotyping array, and the first five principal components to correct for population stratification (see supplementary figure S1). Associations with PM_{10} were additionally adjusted for maternal smoking behaviour during pregnancy based on prenatal urine cotinine measures.

undertaken in a community-based cohort with robust LRTI surveillance and simultaneous measurement of comprehensive risk factors for impaired lung growth. The advantage of using lung function measurements in addition to the broad clinical definition of LRTI or reported wheezing is the continuous data structure and objective measurements, which provide comprehensive measurements of lung health.

Limitations of the study are the potential lack of generalisability to other settings with different exposures; however, many of these exposures are common in LMIC settings. Another limitation is the small sample size with genotype data (n=270). However, by using GRS approaches, we reached a sufficient power to

detect interaction effects [33, 34]. A limitation of our risk score approaches was the validity of the external reference populations: we used a GRS based on samples from European ancestry, which often have a lower predictive performance in non-European ancestry samples [24]. Furthermore, very little is known about the performance of GRSs in populations of mixed ancestry, who are among the most genetically diverse populations globally. In our study, 44% of the infants were of mixed ancestry. In this subgroup, we could not find any gene–environment interactions, which might have at least two possible reasons: 1) infants with Black African ancestry and a genetic predisposition for asthma are more prone to the harmful effects of indoor air pollution than infants of mixed ancestry or 2) the GRS was simply not applicable for infants of mixed ancestry, which is a very heterogenous subgroup with genotypes of varying minor allele frequencies (see the principal component analysis plot in supplementary figure S1). More research is needed on GRS approaches for populations of mixed ancestry.

Conclusions

Pre- and postnatal exposures to PM_{10} and maternal smoking during pregnancy were associated with reduced lung function at 6 weeks and 1 year. We further identified infants with a genetic predisposition for asthma as being a highly susceptible subgroup for the adverse effects of prenatal exposure to indoor air pollution, which highlights the importance of gene–environment interactions for infant lung function.

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Author contributions: A. Hüls planned and conducted the analyses, and was the major contributor in writing the manuscript. P.D. Sly supervised the collection and interpretation of air pollution and lung function data. J.L. MacIsaac, D.T.S. Lin and K.E. Ramadori performed the microarray experiments, which were supervised by M.S. Kobor. H.J. Zar conceived, designed and leads the Drakenstein Child Health Study (DCHS) and obtained funding; D. Gray led and was responsible for the lung function aspects; A. Vanker led and was responsible for the indoor air pollution and environmental tobacco smoke measurements; N. Koen oversaw work on genetics testing in the DCHS; D.J. Stein conceived, designed and led the genetics aspects of the DCHS. All authors contributed to the final paper.

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