Environmental Research 197 (2021) 111169

Contents lists available at ScienceDirect

Environmental Research

journal homepage: www.elsevier.com/locate/envres

Low-level exposure to polycyclic aromatic hydrocarbons is associated with reduced lung function among Swedish young adults

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ARTICLE INFO

Keywords:
Air pollution
Asthma
Urinary metabolites
Environmental exposure
Polycyclic aromatic hydrocarbons

ABSTRACT

Background: Exposure to polycyclic aromatic hydrocarbons (PAHs) has been linked to adverse pulmonary effects. However, the impact of low-level environmental PAH exposure on lung function in early adulthood remains uncertain.

Objectives: To evaluate the associations between urinary PAH metabolites and lung function parameters in young adults.

Methods: Urinary metabolites of pyrene, phenanthrene, and fluorene were analysed in 1000 young adults from Sweden (age 22–25 years) using LC-MS/MS. Lung function and eosinophilic airway inflammation were measured by spirometry and exhaled nitric oxide fraction (FeNO), respectively. Linear regression analysis was used to evaluate associations between PAH metabolites and the outcomes.

Results: Median urinary concentrations of 1-OH-pyrene, ∑OH-phenanthrene, and ∑OH-fluorene were 0.066, 0.36, 0.22 μg/L, respectively. We found inverse associations of ∑OH-phenanthrene and ∑OH-fluorene with FEV1 and FVC, as well as between 1-OH-pyrene and FEV1/FVC ratio (adjusted $P < 0.05$; all participants). An increase of 1% in ∑OH-fluorene was associated with a decrease of 73 mL in FEV1 and 59 mL in FVC. In addition, ∑OH-phenanthrene concentrations were, in a dose-response manner, inversely associated with FEV1 (B from −109 to −48 compared with the lowest quartile of ∑OH-phenanthrene; p trend 0.004) and FVC (B from −159 to −102 compared with lowest quartile; p-trend <0.001). Similar dose-response associations were also observed between ∑OH-fluorene and FEV1 and FVC, as well as between 1-OH-pyrene and FEV1/FVC (p-trend <0.05). There was no association between PAH exposure and FeNO, nor was there an interaction with smoking, sex, or asthma.

Conclusion: Low-level PAH exposure was, in a dose-response manner, associated with reduced lung function in young adults. Our findings have public health implications due to i) the widespread occurrence of PAHs in the environment and ii) the clinical relevance of lung function in predicting all-cause and cardiovascular disease mortality.

1. Introduction

Lung function evaluation is an essential element for diagnosis of respiratory health problems such as asthma and chronic obstructive pulmonary disease (COPD). Reduced lung function is observed with increasing age in the general healthy adult population; however, this reduction is more pronounced in asthma patients (James et al., 2005; Lange et al., 1998). In addition, reduced lung function peak in early

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https://doi.org/10.1016/j.envres.2021.111169
Received 27 November 2020; Received in revised form 15 March 2021; Accepted 8 April 2021
Available online 20 April 2021

adulthood is now established as an important risk factor for later COPD (Agusti and Faner 2019). Epidemiological studies have shown adverse pulmonary effects in relation to air pollution exposure, where measurements of atmospheric nitrogen dioxide, elemental carbon, particulate matter ($PM_{2.5}$ and PM_{10}), ozone, or acid vapor were frequently used for exposure assessment (Fuertes et al., 2015; Gauderman et al., 2004; Schultz et al., 2016). However, the relation between individual-level exposure to polycyclic aromatic hydrocarbons (PAHs) and lung function is not well-characterised (Cakmak et al., 2017; Choi et al., 2013; Zhou et al., 2016).

PAHs are a group of ubiquitous lipophilic chemicals composed of fused aromatic rings (IARC 2010). PAHs can occur naturally, as in fossil fuel, or be formed by incomplete combustion of organic matter including tobacco, wood and petroleum oil (Alegbeleye et al., 2017; IARC 2010). Humans are often exposed to a mixture of PAHs through inhalation, dermal uptake, and ingestion (Kim et al., 2013). Unlike lower-molecular-weight PAHs (LMW-PAHs) that are more volatile (e.g. naphthalene), higher-molecular-weight PAHs (HMW-PAHs) are in the solid state and usually found adsorbed to particulate matter (Oliveira et al., 2019; Srogi 2007). Urinary 1-hydroxypyrene (1-OH-Pyr), a metabolite of pyrene, is considered to be the classical biomarker of PAH exposure; however, metabolites of other PAHs, such as phenanthrene and fluorene, should also be considered, particularly for exposure assessment of LMW-PAHs (Dor et al., 1999; Li et al., 2008).

Numerous investigations have shown carcinogenic potential of PAHs, hence, regulatory agencies including the International Agency for Research on Cancer (IARC) and the US. Environmental Protection Agency (U.S.EPA) have classified several PAHs as human carcinogens or probable/possible carcinogens (Andersson and Achten 2015; IARC 2010). In addition, a few studies have linked PAH exposure to non-carcinogenic respiratory health effects in children, including impaired lung function (Jedrychowski et al., 2015; Majewska et al., 2018; Padula et al., 2015), asthma (Wang et al., 2017), and bronchitis (Hertz-Picciotto et al., 2007). Despite these efforts, the effect of PAH exposure on lung function in early adulthood remains unclear. Accordingly, the aim of this study was to investigate the effect of low-level environmental PAH exposure, measured as urinary metabolites, on lung function parameters in young adults.

2. Methods

2.1. Study population

This is a cross-sectional study based on data from the 24-year follow-up of the Swedish cohort BAMSE (Barn/Child, Allergy, Milieu, Stockholm, Epidemiology). Full details of the BAMSE study have been described elsewhere (Wickman et al., 2002). Briefly, the BAMSE study is a birth cohort comprised 4089 newborns from Stockholm, Sweden, recruited between 1994 and 1996 (baseline) and followed at 1, 2, 4, 8, 12, 16, and 24 years of age, with questionnaire response rate of 96%, 94%, 91%, 84%, 82%, 79%, and 75%, respectively. Clinical examinations have been conducted at 4, 8, 16, and 24 years of age (Melén et al., 2020).

The population of this study comprised 500 female and 500 male participants who completed their questionnaires and donated urine samples during clinical examinations that took place between December 2016 and May 2019. In total, 2233 participants met these criteria, and we included a sex-balanced study group to enable better stratification by sex in the statistical analyses. By design, all participants who had donated a urine sample at age 4 years (n = 546) together with all users of cigarettes (daily), smokeless tobacco (oral moist snuff, snus; daily or occasionally), or e-cigarettes (e-cigs; daily or occasionally) were selected from those who were recruited through January 7, 2019. Applying these selection criteria resulted in 439 females and 429 males. To complement the number of participants to 500 in each sex, we randomly selected 61 females and 71 males from those who had completed questionnaires, attended clinical examinations and gave urine samples, and had information on the use of tobacco products. Oversampling of tobacco users was done to enable stratification by tobacco use. An overview of the selection process is given in Figure S1.

This study was approved by the regional Ethics Committee at Karolinska Institutet in Stockholm, Sweden, and was conducted according to the Declaration of Helsinki. All participants gave a written informed consent.

2.2. Questionnaire and clinical examination

The questionnaire queried information on medical history including respiratory problems, use of medication, life-style factors, and environmental exposures including tobacco use and exposure to secondhand smoke. In addition, data from baseline questionnaire on covariates predictive of lung function were used for statistical adjustment purposes (more details in 2.4 *Statistical Analysis*).

The clinical examination included anthropometry measurements, e.g. height and weight, spirometry testing (forced expiratory volume at 1 s [FEV1] and forced vital capacity [FVC]), measurement of the fractional exhaled nitric oxide concentration (FeNO: a biomarker for eosinophilic pulmonary inflammation as described previously (Wang et al., 2020), and donation of spot urine samples (stored at −80 °C until analysis).

FEV1 and FVC measurements were carried out using the Jaeger MasterScreen-IOS system (Carefusion Technologies, San Diego, CA, USA), and evaluated according to the statements of American Thoracic Society (ATS) and the European Respiratory Society (ERS) (Miller et al., 2005). The ratio FEV1/FVC was then calculated and presented as percentages. FeNO measurement was performed using a chemiluminescence analyser (EcoMedics Exhalyzer® CLD 88sp with Denox 88; Eco Medics, Duernten, Switzerland). Predicted values and z-scores of FEV1, FVC and FEV1/FVC ratio were calculated for each participant using equations from the Global Lung Function Initiative (GLI) according to age, sex, and height (Quanjer et al., 2012).

2.3. Analysis of urinary metabolites

High-performance liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) was used to analyse urinary cotinine and the PAH metabolites; 1-hydroxypyrene (1-OH-Pyr), 1-hydroxyphenanthrene (1-OH-Phe), sum of 2- and 3-hydroxyphenanthrene (∑2,3-OH-Phe), 4-hydroxyphenanthrene (4-OH-Phe), and sum of 2- and 3-hydroxyfluorene (∑2,3-OH-Flu). Details of the method were described previously by Alhamdow et al. (2020) and a modified method was used for cotinine (Shu et al., 2018). Briefly, urine was transferred to 96-well plates and 0.1 mL of ammonium acetate (pH 6.5) and β-glucuronidase (*Escherichia coli*) were added. The solution was incubated for 30 min at 37 °C. Afterwards, deuterium-labeled internal standards for all compounds were added. The samples were analysed using a triple quadrupole linear ion trap mass spectrometer (QTRAP6500+; AB Sciex, Framingham, MA, USA). The metabolites 2-OH-Phe and 3-OH-Phe as well as 2-OH-Flu and 3-OH-Flu could not be separated and were therefore analysed as single peaks (i.e. ∑2,3-OH-Phe and (∑2,3-OH-Flu, respectively). Limit of detection (LOD) values were calculated from chemical blank samples and defined as three times the standard deviation of the concentration corresponding to the peak at the same retention time as the individual compounds. When urine concentrations were below LOD, measured concentrations were used in the statistical analysis (Gyllenhammar et al., 2017). Specific gravity-adjusted PAH metabolite concentrations were used in the main statistical analysis, while creatinine-adjusted concentrations were reported to allow comparison with other studies. Detailed description of the analytical method is provided in the supplementary material (*sample preparation* and Table S1).

2.4. Statistical analysis

Data were presented as frequencies and percentages for categorical variables, or as median (25th-75th percentiles) for continuous variables. Differences between groups were evaluated by chi-squared test (categorical variables) or Kruskal-Wallis H test (continuous variables). Results are presented for the total study population (n = 1000) and per stratum (females versus males, no asthma group versus asthma group, and nonsmokers versus smokers). In order to evaluate potential selection bias, comparisons of basic characteristics between the study population (n = 1000) and the total BAMSE cohort (n = 4089) were performed using a finite population correction factor for calculating 95% confidence intervals (CIs).

FeNO and PAH metabolite data were positively skewed; therefore, natural-log transformation was applied to improve data distribution. The following PAH metabolite variables were used as main predictors; i) 1-OH-Pyr, ii) ∑OH-Phe (sum of 1-OH-Phe, 2- and 3-OH-Phe, and 4-OH-Phe), and iii) ∑OH-Flu (sum of 2-OH-Flu and 3-OH-Flu). Spearman's rank correlation was used to evaluate intercorrelations of PAH metabolites among smokers and nonsmokers.

Linear regression models adjusted for confounders (described below) and stratified by smoking sex, and asthma were fit to explore associations between PAH metabolites as continuous variables and lung function parameters (i.e. FEV1, FVC, FEV1/FVC ratio and their z-scores, and FeNO). In addition, similar models were fit to evaluate exposure-response (dose-response) relationship using categorical PAH metabolite variables (quartiles). Trend test was performed by including the quartile variable of PAH metabolites (4 categories) as a continuous variable in the adjusted linear regression model. Results are presented as unstandardized beta estimate (B) and 95%CIs. Key linear regression assumption of linearity, normal distribution of the residuals and homoscedasticity were adequately met.

Logistic regression analysis was employed to investigate associations between PAH metabolites and asthma (see definition in the supplementary material), adjusting for confounders/covariates and stratifying by sex and smoking status. Results are presented as odds ratios (ORs) and 95%CIs.

Confounders and covariates (see supplementary material for definitions) were selected either based on *a priori* knowledge from previous studies on lung function in BAMSE (Schultz et al., 2018; Thacher et al., 2018) or through backward selection process where a minimum of 10%-change in the estimate was considered for inclusion in the adjusted model. Consequently, the final list of confounders and covariates selected for adjustment was as follows: sex, maternal smoking during pregnancy/infancy, asthma/allergy heredity, and parental socioeconomic status obtained from previous questionnaires (i.e. baseline up to 2 years of age) as well as age, height, cigarette smoking, smokeless tobacco use, and secondhand smoke exposure collected at the latest follow-up. Adjustment for the use of asthma medication (during the past week) was also considered for linear regression models among participants with asthma (n = 103).

Cigarette smoking is a main source of PAH exposure, therefore, sensitivity analyses were carried out among i) tobacco-free participants (i.e. never smokers who had urinary cotinine of <30 μg/L (Kim 2016), and were not using snus, e-cigs, waterpipe, or exposed to secondhand smoke [n = 400]), ii) smokers with additional adjustment for number of cigarettes/day, and iii) smokers who were not using snus, e-cigs, waterpipe, or exposed to secondhand smoke with additional adjustment for urinary cotinine concentrations.

P-values <0.05 were considered statistically significant. Statistical analyses were performed using the STATA software (version 16; Stata Corp., College Station, TX, USA).

3. Results

3.1. Basic characteristics

The distribution of background characteristics did not differ between the study population (n = 1000) and the total BAMSE population (n = 4089), apart from a slightly higher prevalence of asthma/allergy heredity (32.2% versus 29.7%) and infant eczema (29.5% versus 25.8%) (Table S2). In the study population, the median age was similar in females and males (22.6 years; range 22–25 years). Higher prevalence of cigarette smoking (32.0%) and asthma (16.2%), but lower prevalence of snus use (13.2%) was observed in females compared with males (23.0%, 11.2%, 38.6%, respectively) (Table 1). It is important to note that tobacco users in this study were oversampled by design. Details about other basic characteristics are described in Table 1. Median FEV1 and FVC were 3482 mL and 4108 mL in females and 4707 mL and 5812 mL in males, respectively (Table 1). Median z-scores of FEV1 and FVC were −0.14 and 0.013 in females and −0.42 and −0.16 in males, respectively (Table 1).

3.2. Urinary PAH metabolites

Urinary concentrations were lowest for 4-OH-Phe and 1-OH-Pyr (11% and 53% of the analysed samples were above LOD, respectively), but highest for ∑OH-Flu and other phenanthrene metabolites (≥81% of the samples above LOD, Table S1). Female participants had slightly higher median PAH metabolite concentrations of 1-OH-Pyr (0.071 μg/L), ∑OH-Phe (0.39 μg/L), and ∑OH-Flu (0.24 μg/L), compared with males (0.057 μg/L, 0.34 μg/L, 0.21 μg/L, respectively; $P < 0.05$; Table 1). Creatinine-adjusted concentrations were also reported to allow comparisons with other studies (Table S3). All PAH metabolites were moderately intercorrelated ($P < 0.001$), and the strongest correlation was observed between ∑OH-Phe and ∑OH-Flu among nonsmokers ($r_s = 0.67$; Table S4).

3.3. Associations of PAH metabolites with FEV1 and FVC

Associations between PAH metabolites and the lung function parameters FEV1 and FVC are presented in Fig. 1a and b. Adjusted linear regression analyses showed inverse associations between ∑OH-Phe and FEV1 (B [95%CI] = −59 mL [–97, −20]) and FVC (−51 mL [–98, −4.5]), as well as between ∑OH-Flu and FEV1 (−73 mL [–115, −30]) and FVC (−59 mL [–111, −6.5]). The latter estimates, for example, can be translated as follows: 1% increase in the urinary concentrations of ∑OH-Flu is associated with a decrease of 73 mL in FEV1 and 59 mL in FVC. However, 1-OH-Pyr was associated with neither FEV1 nor FVC. Stratified analyses showed that these inverse associations were comparable among smoking and nonsmoking participants (Fig. 1a and b), males and females (Figure S2a–b), and participants with and without asthma (Figure S2a–b). For example, adjusted B (95%CI) of the association between ∑OH-Flu and FEV1 was −64 mL (−120, −8.1) in nonsmokers, and −77 mL (−145, −9.7) in smokers (Fig. 1a and b). In addition, there were no statistically significant interactions between ∑OH-Phe or ∑OH-Flu and smoking, sex, or asthma (data not shown). Moreover, linear regression analyses of PAH metabolites with the z-scores of FEV1 and FVC showed similar results (Table S5).

Sensitivity analysis among tobacco-free participants showed attenuated inverse associations of ∑OH-Phe and ∑OH-Flu with FEV1 ($P > 0.05$), compared with the associations in the total study population (Figure S3). Among smokers, the estimates of the associations of ∑OH-Phe and ∑OH-Flu with FEV1 and FVC increased when additionally adjusting for the number of cigarettes per day or for urinary cotinine (only ∑OH-Flu; Figure S3). For instance, B (95% CI) for the association between ∑OH-Flu and FEV1 was −77 mL (−145, −9.7) without additional adjustment (Fig. 1a), −130 mL (−216, −44) when further adjusting for the number of cigarettes per day (Figure S3a), and −143

Table 1
Basic characteristics of study population.

	Total		Female		Male		*P* value[e]
	N	Median (Q1, Q3)	n	Median (Q1, Q3)	n	Median (Q1, Q3)	
Continuous variables							
Age (year)	1000	22.6 (22.3, 22.8)	500	22.6 (22.3, 22.8)	500	22.6 (22.3, 22.9)	0.64
Height (m)	1000	1.75 (1.68, 1.82)	500	1.68 (1.64, 1.72)	500	1.82 (1.77, 1.87)	<0.001
BMI (kg/m^2)	1000	22.7 (20.8, 25.0)	500	22.2 (20.3, 24.5)	500	23.2 (21.4, 25.3)	<0.001
1-OH-Pyr (μg/L)	998	0.066 (<LOD, 0.11)	499	0.071 (<LOD, 0.12)	499	0.057 (<LOD, 0.10)	0.006
1-OH-Phe (μg/L)	996	0.16 (0.10, 0.27)	498	0.17 (0.11, 0.29)	498	0.15 (0.086, 0.25)	0.001
∑2,3-OH-Phe (μg/L)	996	0.18 (0.11, 0.29)	498	0.19 (0.11, 0.28)	498	0.17 (0.12, 0.30)	0.84
4-OH-Phe (μg/L)	996	<LOD (<LOD, <LOD)	498	<LOD (<LOD, <LOD)	498	<LOD (<LOD, <LOD)	NA
∑OH-Phe (μg/L)	996	0.36 (0.23, 0.60)	498	0.39 (0.25, 0.60)	498	0.34 (0.22, 0.60)	0.022
∑2,3-OH-Flu (μg/L)	996	0.22 (0.15, 0.38)	498	0.24 (0.16, 0.43)	498	0.21 (0.14, 0.35)	<0.001
Cotinine (μg/L)	1000	7.8 (1.3, 2004)	500	4.4 (1.4, 801)	500	81 (1.2, 3033)	<0.001
Number of cigarettes per day[f]	264	3.0 (0.71, 9.5)	153	4.0 (1.0, 9.0)	111	3.0 (0.57, 10)	0.37
FEV1 (mL)	894	4012 (3455, 4696)	460	3482 (3205, 3770)	434	4707 (4319, 5065)	<0.001
FVC (mL)	894	4785 (4073, 5781)	460	4108 (3753, 4461)	434	5812 (5267, 6295)	<0.001
FEV1/FVC (%)	894	83 (79, 88)	460	85 (82, 89)	434	81 (77, 86)	<0.001
FEV1 z-score	894	−0.28 (−0.84, 0.31)	460	−0.14 (−0.74, 0.38)	434	−0.42 (−0.94, 0.20)	<0.001
FVC z-score	894	−0.083 (−0.60, 0.57)	460	0.013 (−0.57, 0.58)	434	−0.16 (−0.65, 0.51)	0.14
FEV1/FVC z-score	894	−0.42 (−0.93, 0.21)	460	−0.29 (−0.85, 0.28)	434	−0.53 (−1.0, 0.12)	0.002
FEV1% predicted	894	97 (90, 104)	460	98 (91, 104)	434	95 (89, 102)	<0.001
FVC % predicted	894	99 (93, 107)	460	100 (93, 107)	434	98 (92, 106)	0.14
FEV1/FVC % predicted	894	97 (93, 102)	460	98 (94, 102)	434	96 (92, 101)	<0.001
FeNO (ppb)	884	12 (8, 19)	449	10 (7, 14)	435	14 (10, 22)	<0.001
Categorical variables							
	n (%)		***n (%)***		***n (%)***		
Parental socioeconomic status (white collar worker)	812 (82.5)		404 (81.9)		408 (83.1)		0.63
Asthma/allergy heredity (yes)[a]	319 (32.2)		166 (33.7)		153 (30.7)		0.30
Maternal smoking during pregnancy/infancy (yes)	144 (14.4)		78 (15.6)		66 (13.2)		0.28
Maternal age (<25 years)	73 (7.3)		36 (7.2)		37 (7.4)		0.90
Exclusive breast feeding (≥4 months)	757 (77.5)		372 (76.1)		385 (78.9)		0.24
Infant wheeze (yes)	264 (27.4)		117 (24.3)		147 (30.5)		0.030
Infant eczema (yes)	284 (29.5)		156 (32.5)		128 (26.5)		0.041
Asthma (yes)[b]	137 (13.7)		81 (16.2)		56 (11.2)		0.022
Smoker (yes)[c]	275 (27.5)		160 (32)		115 (23)		0.002
Snus use (yes)	259 (25.9)		66 (13.2)		193 (38.6)		<0.001
E-cigarette use (yes)	80 (8.0)		27 (5.4)		53 (10.6)		0.002
Waterpipe use (yes)	26 (2.6)		11 (2.2)		15 (3.0)		0.42
Secondhand smoke exposure (yes)	39 (4.0)		24 (4.9)		15 (3.1)		0.14
Physical activity (high)[d]	730 (85.4)		352 (83.4)		378 (87.3)		0.11
Education (university or higher)	361 (36.2)		202 (40.5)		159 (31.9)		0.005
Employment							
Employed	439 (43.9)		218 (43.6)		221 (44.2)		0.039
Student	487 (48.7)		255 (51)		232 (46.4)		
Other	74 (7.4)		27 (5.4)		47 (9.4)		

Abbreviations: BMI (body-mass index), FEV1 (forced expiratory volume at 1 s), FVC (forced vital capacity), FeNO (fractional exhaled nitric oxide), ppb (part per billion), OH-Pyr (hydroxypyrene), OH-Phe (hydroxyphenanthrene), ∑2,3-OH-Flu (sum of 2- and 3-OH-hydroxyfluorene), and ∑OH-Phe (sum of 1-OH-Phe, 2- and 3-OH-Phe, and 4-OH-Phe). Z-scores for FEV1, FVC and FEV1/FVC ratio were calculated using equations from the Global Lung Function Initiative (GLI) according to age, sex, and height.

[a] Defined as the mother and/or the father had i) a doctor-diagnosed asthma combined with asthma medication, and/or ii) a doctor-diagnosed hay fever combined with furred-pets and/or pollen allergy, at baseline questionnaire.

[b] Participants were defined as having asthma if they ever had a doctor-diagnosed asthma, together with i) experience of breathing difficulties during the past 12 months prior to recruitment, or ii) occasional/regular use of asthma medicines during the past 12 months.

[c] Daily and occasional smokers were categorized as "smoker".

[d] Fulfilling the Swedish recommendations of physical activity ("high" means ≥ 2.5 h/week of moderate to vigorous activity or 1.25 h/week of vigorous activity).

[e] Mann-Whitney *U* test (continuous variables) and chi-squared test (categorical variables).

[f] Median number of cigarettes per day among smokers (daily and occasional smokers).

mL (−254, −32) when further adjusting for urinary cotinine, instead of number of cigarettes per day (Figure S3a). Dose-response relationship was observed between increasing urinary concentrations of ∑OH-Phe and ∑OH-Flu (the first quartile as a reference category) and decreasing FEV1 and FVC (*P*-trend <0.05, adjusted for confounders; Fig. 2a and b). For example, compared with the 1st quartile of ∑OH-Flu, B of the association between ∑OH-Flu and FEV1 was −102 mL for the 2nd quartile, −129 mL for the 3rd quartile, and −159 mL for the 4th quartile (Fig. 2a and b).

3.4. Associations of PAH metabolites with FEV1/FVC ratio and FeNO

An inverse association was observed between 1-OH-Pyr and FEV1/FVC ratio (B −0.56, 95%CI −0.96 to −0.17; Fig. 1c). When stratifying by smoking, similar patterns were shown, although not statistically significant among smokers (B −0.61, 95%CI −1.1 to −0.14 for nonsmokers, and −0.40, −1.2 to 0.37 for smokers; Fig. 1c). In addition, dose-response relationship was also observed between 1-OH-Pyr (the first quartile as a reference category) and decreasing FEV1/FVC ratio (adjusted *P*-trend = 0.015; Fig. 2c). No significant associations were observed between ∑OH-Phe and ∑OH-Flu and FEV1/FVC ratio, or between all PAH metabolites and FeNO, except for ∑OH-Flu in smokers (B −0.12, 95%CI

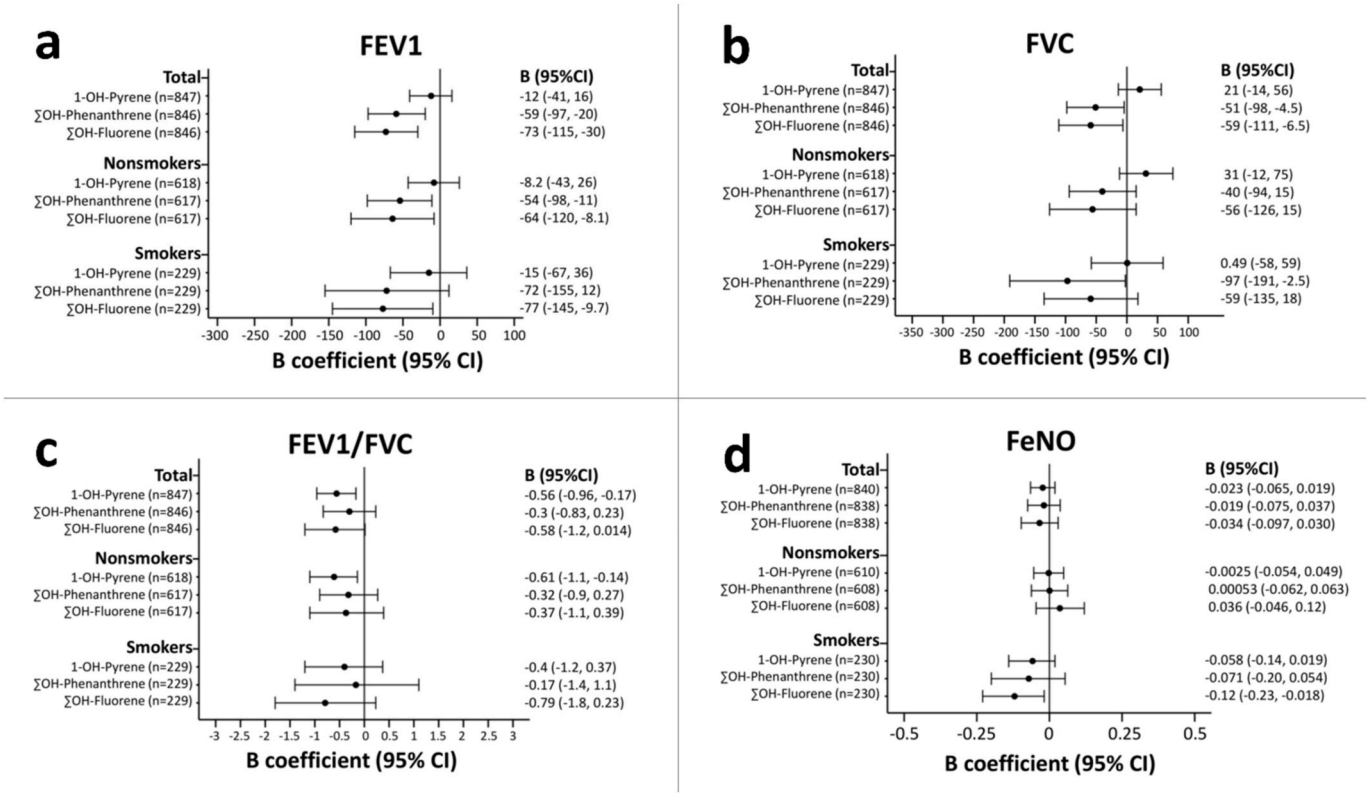

Fig. 1. Adjusted linear regression models of PAH metabolites (natural log-transformed continuous variables) with lung function parameters; **a**) FEV1 (forced expiratory volume at 1 s; continuous variable), **b**) FVC (forced vital capacity; continuous variable), **c**) FEV1/FVC % (continuous variable), and **d**) FeNO (fractional exhaled nitric oxide concentration; natural log-transformed continuous variable). Analysis is shown for the total study population, nonsmokers (never and former smokers), and smokers (occasional and daily smokers). Results are presented as unstandardized beta estimate (B) and 95% confidence interval (95%CI). Models were adjusted for maternal smoking during pregnancy/infancy, asthma/allergy heredity, parental socioeconomic status, sex, age, height, smoking status (only for the total study population), use of smokeless tobacco (snus), and secondhand smoking.

–0.23 to −0.018; Figs. 1d and 2d).

3.5. Associations of PAH metabolites with asthma

Urinary 1-OH-Pyr was associated with higher odds of asthma among smokers (adjusted OR 1.53, 95% CI 1.04 to 2.23), while no statistically significant associations were observed among non-smokers or total study population (Figure S4). However, no statistically significant interaction was observed between 1-OH-Pyr and smoking status in relation to asthma (*P* for interaction >0.05). Furthermore, no significant associations were observed between ∑OH-Phe or ∑OH-Flu and asthma (Figure S4).

4. Discussion

In a population-based sample of young adults with a narrow age range (22–25 years), we found a dose-response relationship between low-level PAH exposure and reduced lung function. Even though smoking is a main source of PAH exposure, the associations were indicated in smokers as well as nonsmokers. This indicates that PAH exposure might adversely affect lung function, independent of source of exposure. Our findings have significant public health implications due to the widespread occurrence of PAHs in the environment, and a high clinical relevance as impaired lung function has been shown to be predictive of all-cause and cardiovascular mortality (Bang et al., 1993; Kannel et al., 1983; Schünemann et al., 2000; Sin et al., 2005).

Despite the fact that PAHs are potent environmental pollutants, limited research has focused on the effect of PAHs on lung function in the general population, particularly in early adulthood. In the absence of PAH occupational exposure and smoking, the general population is mainly exposed to PAHs through inhalation of contaminated ambient air, where PAHs are primarily bound to particulate matter, and/or ingestion of broiled, grilled, fried, smoked, or baked food (Dobraca et al., 2018; IARC 2010). PAH exposure levels in our study were low and comparable to those reported by a previous study including a group of non-occupationally exposed male individuals from Sweden (median age 43 years), in which median concentrations of 1-OH-Pyr, ∑2,3-OH-Phe, and ∑2,3-OH-Flu were 0.06, 0.27, and 0.15 μg/g creatinine, compared with 0.057, 0.33, and 0.20 μg/g creatinine in our study, respectively (Alhamdow et al., 2017, 2020). It is thus interesting to observe an association with lung function at such low levels of PAH exposure. Despite that PAH-related pulmonary adverse effects have been a consistent finding in the literature, the associations between HMW-PAHs (e.g. pyrene) or LMW-PAHs (e.g. phenanthrene and fluorene) with lung function parameters were heterogeneous.

A recent repeated measures study from China (community sample; n = 191) found inverse associations of ∑2,3-OH-Phe with FEV1 and FVC, and 1-OH-Pyr with FEV1 ($P < 0.05$). However, ∑2,3-OH-Flu was not associated with lung function parameters (Hou et al., 2020). Another community-based study from China (n = 314) evaluating $PM_{2.5}$-bound PAHs showed inverse associations of fluoranthene and pyrene with FEV1, as well as naphthalene, fluoranthene, acenaphthene, and pyrene with FVC (Mu et al., 2019a). Further, a study including 3749 participants from the Chinese general population showed inverse associations between the sum of different urinary metabolites of PAHs (pyrene, phenanthrene, fluorene, and naphthalene) with FEV1 and FVC, but not with FEV1/FVC ratio (Mu et al., 2019b). Similar to what we found in the current study, the associations remained significant among nonsmokers ($P < 0.05$) (Mu et al., 2019b). Inverse associations of several urinary PAH metabolites, including metabolites of pyrene, phenanthrene, and

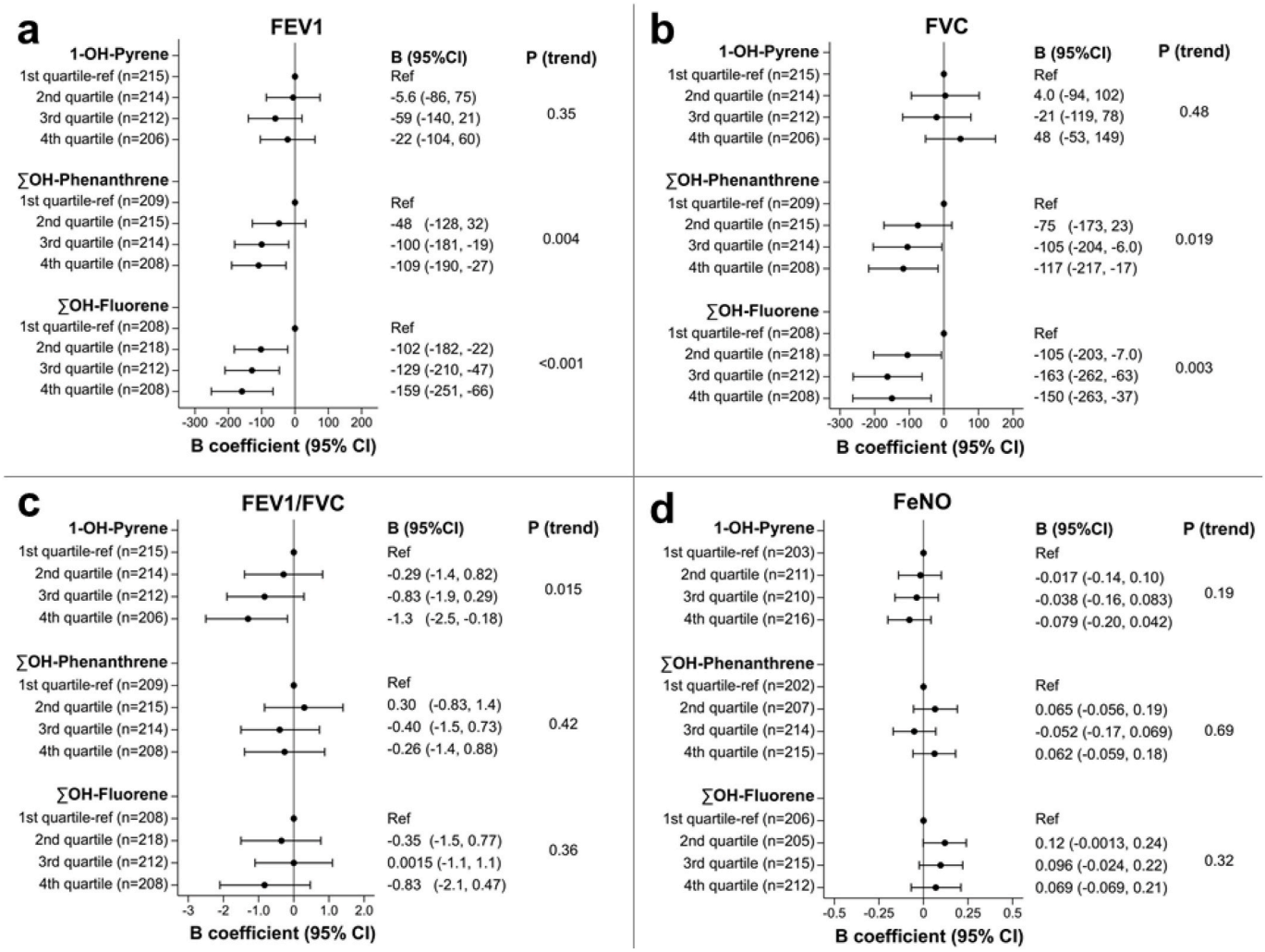

Fig. 2. Exposure-response analysis for the associations of PAH metabolites (quartiles) with the lung function parameters **a**) FEV1 (forced expiratory volume at 1 s, continuous variable), **b**) FVC (forced vital capacity, continuous variable), **c**) FEV1/FVC ratio % (continuous variable), and **d**) FeNO (fractional exhaled nitric oxide concentration, natural log-transformed continuous variable), using adjusted linear regression analyses. Models were adjusted for maternal smoking during pregnancy/infancy, asthma/allergy heredity, parental socioeconomic status, sex, age, height, smoking status, use of snus, and secondhand smoking. Results are presented as unstandardized beta estimate (B) and 95% confidence interval (95%CI). *P* value of trend test was derived from similar adjusted linear regression models where the variable of PAH metabolite quartiles (4 categories) was treated as continuous variable.

fluorene, with FEV1 and FVC were also found in another study in the Chinese general population (n = 2747) (Zhou et al., 2016). The associations of the sum of all urinary metabolites with FEV1 and FVC remained among nonsmokers, although marginally significant for FEV1 (Zhou et al., 2016). In addition, a study in the nonsmoking Canadian general population (n = 3531) reported inverse associations of urinary ∑OH-Phe, ∑OH-Flu, and ∑OH-naphthalene with both FEV1 and FVC, but not with FEV1/FVC ratio (Cakmak et al., 2017). The authors did not find any association between PAH metabolites and the ratio FEV1/FVC, or between 1-OH-Pyr and FEV1 or FVC (Cakmak et al., 2017). Nevertheless, an inverse association between 1-OH-Pyr and FEV1/FVC ratio was observed in a study among older adults (n = 422) from Korea (Choi et al., 2013). It therefore remains to be determined whether LMW-PAHs or HMW-PAHs are more toxic to the lung, and whether certain PAHs play a role in the pathophysiology of restrictive and/or obstructive lung diseases. Even though our study supports the notion that both LMW-PAHs (phenanthrene and fluorene) and HMW-PAHs (pyrene) that are classified by IARC in Group 3 (*not classifiable as to its carcinogenicity to humans*) may adversely affect the respiratory system, the results should be interpreted cautiously due to the low urinary levels of PAH metabolites, 1-OH-Pyr in particular.

The fractional exhaled nitric oxide concentration (FeNO) is a biomarker for eosinophilic airways inflammation (Kharitonov and Barnes 2000). Positive associations between FeNO and urinary metabolites of phenanthrene, but negative associations with metabolites of naphthalene, were observed in a study from China including 4133 participants from the Wuhan-Zhuhai cohort (Zhou et al., 2018). Interestingly, the authors found inverse associations between individual and sum of urinary PAH metabolites (pyrene, phenanthrene, and fluorene) and FeNO among current/former smokers, but positive associations among never smokers. In our study, we found inverse associations between fluorene metabolites and FeNO only among smokers, but no association was found among nonsmokers or in the overall dataset. The associations among smokers can possibly be explained by the high NO concentrations in the cigarette smoke, which may ultimately lead to reduced pulmonary NO production due to the negative feedback loop (Sundy et al., 2007).

The underlying mechanism of the association between PAHs and impaired pulmonary function is largely unknown. PAHs are metabolised by the cytochrome P450 (CYP) enzymes CYP1A1, CYP1A2, and CYP1B1, which are expressed not only in the liver, but also in the lungs (IARC 2010; Shimada and Fujii-Kuriyama 2004). This can result in reactive

PAH metabolites (e.g. radical cations, diol-epoxides, and quinones) that are capable of inducing oxidative stress and causing cellular toxicity (Gurbani et al., 2013; Moorthy et al., 2015). A study among kindergarten children found a mediation effect of 8-Oxo-2′-deoxyguanosine, a biomarker of oxidative stress, on the association between urinary 1-OH-Pyr and asthma (Wang et al., 2017). As well, a study among coke oven workers showed association between increased urinary PAH metabolites and oxidative DNA and lipid damage (Kuang et al., 2013). Inflammation can also play an important role in PAH-induced impaired lung function, as suggested by animal studies (Gentner and Weber 2011; Hussain et al., 2014; Ma et al., 2020; Zhang et al., 2016). it is therefore plausible that PAHs adversely affect the pulmonary epithelia through oxidative stress and inflammation caused by reactive PAH metabolites (Borm et al., 1997; Cioroiu et al., 2013; Farmer et al., 2003; Hussain et al., 2014; Marie-Desvergne et al., 2010; Miller and Ramos 2001). Taken together, our findings primarily suggest general effects of PAHs on lung volumes, since both FEV1 and FVC were affected, rather than an association with airway inflammation and obstructive disease.

Our study holds several strengths. Participants were selected from the well-characterised birth cohort BAMSE, which gave us access to a myriad of information that was used to control for potential confounders. Another advantage is the large sample size (n = 1000), which enabled us to perform the subgroup statistical analysis while maintaining the statistical power. In addition, age-related differences in metabolism of PAHs or lung function development were minimal due to the narrow age range of study population (22–25 years). However, a few limitations should be acknowledged. This study does not address causality between PAH exposure and reduced lung function due to the cross-sectional design. In addition, a single measurement of urinary PAH metabolites might not reflect the long-term PAH exposure of the study population. However, in a study among pre- and peri-pubertal girls exposed to environmental PAHs in Northern California, Dobraca and colleagues showed that a single measurement of urinary PAH metabolites may reflect a multi-year exposure due to the modest variability of environmental PAH exposure over time (Dobraca et al., 2018). Another issue is that unmeasured concurrent exposures, such as particulate matter from air pollution and combustion gases, may contribute to the associations observed. For example, short-term exposure to $PM_{2.5}$ as well as long-term exposure to PM_{10} have been associated with reduced lung function (Adam et al., 2015; Schikowski et al., 2005). It is therefore difficult to estimate the exact effect of each exposure on the outcome. Nevertheless, PAHs may play a role in the pathophysiology of pulmonary function impairment.

5. Conclusions

This study showed that low-level PAH exposure was, in a dose-response manner, associated with reduced lung function in young adults. Our findings have public health implications due to the widespread occurrence of PAHs in the environment, and the well-known clinical relevance of reduced peak lung function for cardio-respiratory disease across the life-course.

Authors contribution

Ayman Alhamdow, Conceptualization, Formal analysis, Methodology, Visualization, and Writing- original draft preparation. Anna Zettergren, Data curation and Writing – review & editing. Inger Kull, Conceptualization, Funding acquisition, Methodology, Resources and Writing – review & editing. Jenny Hallberg, Data curation, Investigation and Writing – review & editing. Niklas Andersson, Data curation, Validation and Writing – review & editing. Sandra Ekström: Data curation, Investigation and Writing – review & editing. Marika Berglund: Conceptualization, Funding acquisition and Writing – review & editing. Craig E. Wheelock: Writing – review & editing. Yona J. Essig: Methodology and Writing – review & editing. Annette M. Krais: Methodology and Writing – review & editing. Antonios Georgelis: Resources and Writing – review & editing. Christian H. Lindh: Funding acquisition, Methodology and Writing – review & editing. Erik Melén: Conceptualization, Funding acquisition, Methodology, Resources and Writing – review & editing. Anna Bergström: Conceptualization, Funding acquisition, Methodology, Project admiration, Resources, Supervision and Writing – review & editing, All authors have read the manuscript and agreed to its content.

Funding and ethical approval

This study was financially supported by the Swedish Research Council; the Swedish Heart and Lung Foundation; the Swedish Research Council for Sustainable Development (FORMAS, grant nuber 2016-01646); the Swedish Research Council for Working Life and Social Welfare; the Swedish Asthma and Allergy Association Research Foundation; the Swedish Environmental Protection Agency (grant numbers NV-09284-13 and NV-00175-15); Region Stockholm (ALF project, and for cohort and database maintenance); and the European Research Council (grant number 757919). Yona J. Essig was supported by a fellowship from the German Research Foundation (DFG).

This study was approved by the regional Ethics Committee at Karolinska Institutet in Stockholm, Sweden.

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.

Acknowledgements

We thank the participants and parents of the BAMSE study, as well as all staff worked with the BAMSE cohort throughout the years. A special thank you to the laboratory staff, Anna Rönnholm, Hamideh Rastkhani och Marie Bengtsson, at the Division for Occupational and Environmental Medicine at Lund University for excellent contribution in the laboratory.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2021.111169.

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