Polycyclic aromatic hydrocarbon exposure and pediatric asthma in children: a case–control study

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Abstract

Background: Bronchial asthma is one of the most prevalent diseases in Arab children. Environmental pollution has been suggested to be considered causative of asthma, nasal symptoms and bronchitis in both children and adult. The objectives of this study were to evaluate the association between serum polycyclic aromatic hydrocarbons (PAHs) levels, asthma and allergic outcomes among Saudi children aged up to 15 yrs. We hypothesized that increased serum PAHs are associated with allergy, asthma, or respiratory symptoms.

Methods: A total of 195 Saudi children (98 asthma pediatric patients and 97 healthy controls) were randomly selected from the Riyadh Cohort Study for inclusion. The diagnosis of Asthma was based on established pediatric diagnosis and medications taken.

Results: Asthma related markers showed highly significant differences between children with and without asthma. Thus IgE, resistin and IL-4 were significantly increased (p < 0.004, 0.001 and 0.003, respectively) in children with asthma compared with non-asthma control subjects. GMCSF, IFN-γ, IL-5, IL-8 and IL-10, on the other hand, were significantly decreased in children with asthma (p < 0.003, 0.03, 0.001, 0.004 and 0.03, respectively). Strong associations between serum PAHs levels and biomarkers of childhood asthma were detected in Arabic children. Data confirmed the role of naphthalene, 4H-cyclobenta[def]phenanthrene, 1,2-benzanthracene, chrysene and benzo(e) acephenanthrylene in childhood asthma; levels of these PAHs were correlated with asthma related biomarkers including IgE, resistin, GMCSF and IFN-γ as well as IL-4, IL-5, IL-8 and IL-10 cytokines.

Conclusions: This data highlight the pivotal role of specific PAHs in childhood asthma.

Keywords: PAHs, Environmental pollution, Childhood asthma, Biomarkers
particles, trace metals, volatile organic compounds, nitrogen dioxide, particulate matter, and PAHs in the development of respiratory symptoms, asthma or the onset of allergies. Studies have shown that exposure to PAHs be associated with adverse respiratory health outcomes. Previous data reported that exposure to PAHs such as benz[a]anthracene, benzo[a]pyrene, benzo[b]fluoranthene, benzo[g,h,i]perylene, chrysene and dibenz[a,h]anthracene are associated with increased cough and wheeze at age 12 months, and breathing problems as well as development of asthma [24,25]. Notably, PAHs exposure was suggested to favor proallergic immunoglobulin IgE responses. Recently, the U.S. National Health and Nutrition Examination Survey (NHANES) (1999–2000, 2001–02) provided comprehensive descriptions of reference ranges for a larger panel of PAHs metabolites collected from a population of children and adults without suspected occupational exposures [20,22]. Higher levels were detected among children, suggesting that they may be at greater risk for adverse health effects. The objectives of this study were to evaluate the association between serum PAHs level with asthma among Saudi children up to 8 yrs. Our starting hypothesis being that increased serum PAHs are associated with allergy, asthma, or respiratory symptoms.

**Methods**

**Study subjects**
A total of 195 Saudis children aged 15 years old and below (98 asthma pediatric patients and 97 healthy controls) were randomly selected from the Riyadh Cohort Study for inclusion. The parent or guardian of each child was asked to answer a questionnaire consisting of demographic information which included dietary questions, area of residence (near the factory, high-traffic area, etc.), presence of a smoker at home and other pertinent questions related to asthma. Asthma was based on established pediatric diagnosis and medications taken. Since most of the subjects were asymptomatic during the course of the study, parents were asked if the child had history of wheezing upon exhalation, frequent episodes of chest tightness and hyper-expansion of thorax with use of accessory muscles. Ethical approval was granted by the Ethics Committee of the College of Science Research Center, King Saud University, Riyadh, KSA.

**Anthropometrics**
Anthropometry included height (rounded off to the nearest 0.5 cm) and weight (rounded off to the nearest 0.1 kg), which were measured using an appropriate international standard scale (Digital Person Scale; ADAM Equipment, Milford, CT, USA), as well as waist and hip circumference in centimeters, which were measured using a standard tape measure; and body mass index (BMI) was calculated as kg/m². The Holtain Khan abdominal caliper by Holtain Ltd (Crymych, UK) was used to measure sagittal abdominal diameter (SAD).

**Biochemical parameters**
Fasting blood was collected by an assigned physician at their respective primary healthcare centers. Blood was drawn, centrifuged and processed on the same day. Both whole blood and serum were placed in plain polystyrene tubes. Serum was delivered to Biomarker Research Program (BRP) for storage at −20°C. Fasting serum glucose levels, and complete lipid profile (triglycerides, total cholesterol, high density lipoprotein [HDL]-cholesterol) were determined using a biochemical analyzer (Konelab, Espoo, Finland). Low density lipoprotein (LDL)-cholesterol was calculated using Friedman formula. This biochemical analyzer was calibrated routinely prior to the analysis of all serum samples using quality control samples provided by the manufacturer (Thermo-Fisher Scientific, Espoo, Finland). LINCOplex, human multiplex immunoassay kit based on Luminex 100 system platform (Luminex Corporation, Austin, TX, USA) was used for determination of three different panels by simultaneous detection of a great variety of cytokines, interleukins and immunoglobulins. The standard protocol for the process was followed. The concentrations of analyte in each sample were calculated with a five parameter model using Luminex IS software ver. 2.3.

**PAH analysis**
A stock solution of 12 PAHs mixed standard solutions was prepared by dissolving 1 mg from each PAH in 100 ml acetonitrile. The series of PAHs mix standard (0.0, 0.5, 2.5, 5, 10, 50 and 100 ng ml⁻¹) were prepared in acetonitrile for linearity. Calibration curves were generated by plotting peak area versus concentration. Each subject's sample was analyzed for a suite of 12 PAHs as previously described [23]. Analytical determination was conducted by using liquid-liquid extraction followed by high performance liquid chromatography with fluorescence detector (HPLC-FLD). Standard calibration curve was presented excellent linearity, with good separation and repeatability. The limit of detection (LOD) was defined as the higher value of either the method blank LOD (three times standard deviation of method blank after subtracting the average blank), or the instrument LOD (signal >3 times the signal to noise ratio). The limit of quantification (LOQ) (signal >10 times the signal to noise ratio). The limits of detection were ranged from 1.2 to 4.0 ng ml⁻¹ (0.001 ppm). The lowest possible standard on the calibration curve was accepted as the LOQ. The calibration curve and recovery validation study were all repeated three times (n = 3). Recovery and precision were estimated by using spiked blank matrix, samples were analysed in duplicate at five levels...
spread equally over the analytical range. The recoveries were calculated from the analytical signal as the ratio between found and expected expressed in %. The rate of recovery for all 12 PAHs were ranged from 86 to 106%.

Statistical analysis
Data represented by mean ± standard deviation. Skewed data was either log or square root transformed. Non Gaussian variables were represented by median and inter quartile ranges. Two samples independent T test was performed to compare control and asthma. Mann Whitney U test was performed to compare control and asthmatic, wherever variables don’t follow Gaussian distribution. P values <0.05 were considered statistically significant. Pearson’s correlation test was performed to examine various correlations. Analyses were performed with the SPSS-PC software, version 16.0 (SPSS Inc, Chicago, IL).

Results

Subjects characteristics
The epidemiological characterization of the 195 Saudis children included in the study (98 asthma pediatric patients and 97 non-asthma control subjects) is provided in Table 1. All children were comparable regards to BMI, waist, SAD, total cholesterol, glucose, triglycerides and LDL-cholesterol.

Association between PAH and asthma markers
Not surprisingly, asthma related biochemical markers showed highly significant differences between children with asthma and non-asthma control subjects. Thus, compared to non-asthma control subjects significant increase in level of IgE (123.1 ± 5.0 vs. 61.1 ± 4.3, p = 0.004), resistin (24.5 ± 1.6 vs. 17.3 ± 1.3, p = 0.001) and IL-4 (18.5 ± 3.6 vs. 9.2 ± 1.4, p = 0.003) and IL-8 (6.3 ± 1.2 vs. 12.4 ± 1.8, p = 0.004) and IL-10 (9.2 ± 1.4 vs. 12.1 ± 1.7, p = 0.03) pg ml⁻¹. While there was significant decrease in levels of GMCSF (1.0 ± 0.11 vs. 1.9 ± 0.1, p = 0.003), IFN-γ (1.6 ± 0.63 vs. 2.4 ± 0.74, p = 0.03), IL-5 (0.52 ± 0.17 vs. 0.92 ± 0.2, p = 0.001), IL-8 (6.3 ± 1.2 vs. 12.4 ± 1.8, p = 0.004) and IL-10 (9.2 ± 1.4 vs. 12.1 ± 1.7, p = 0.03) pg ml⁻¹.

Quantification of PAHs showed the presence of significant difference between children with asthma and non-asthma control subjects in levels of naphthalene (26.2 ± 2.5 vs. 10.7 ± 2.7, p = 0.006), 4H-cyclobenta[def]phenanthrene (4.8 ± 0.93 vs. 2.1 ± 0.80, p = 0.02) ng ml⁻¹. In contrast with these results, no differences were detected between the two groups in the levels of anthracene, phenanthrene, fluoranthene and benzo(a)pyrene.

Table 1 Characterization of asthmatic children compared to non-asthma control subjects

| Parameters                  | Control | Asthma  | P value |
|-----------------------------|---------|---------|---------|
| Age (years)                 | 13.5 ± 4.2 | 13.7 ± 2.9 | 0.81    |
| BMI (kg/m²)                 | 21.1 ± 5.5 | 21.3 ± 6.6 | 0.81    |
| Waist circumference (cm)    | 66.6 ± 15.1 | 70.7 ± 17.1 | 0.09    |
| Hip circumference (cm)      | 82.1 ± 20.7 | 83.8 ± 19.9 | 0.54    |
| SAD (cm)                    | 17.0 ± 7.5 | 17.7 ± 19.6 | 0.53    |
| Cholesterol (mmol/l)        | 4.3 ± 0.88 | 4.1 ± 0.72 | 0.07    |
| Glucose (mmol/l)            | 5.3 ± 1.7  | 5.3 ± 1.7  | 0.90    |
| HDL-Cholesterol (mmol/l)    | 1.04 ± 0.34 | 0.90 ± 0.31 | 0.008   |
| Triglycerides (mmol/l)      | 1.1 ± 0.60 | 1.03 ± 0.41 | 0.59    |
| LDL-Cholesterol (mmol/l)    | 2.8 ± 0.80 | 2.7 ± 0.67 | 0.21    |
| IgE (pg/ml)                 | 61.1 ± 4.3 | 123.1 ± 50  | 0.004   |
| Resistin (pg/ml)            | 17.3 ± 1.3 | 24.5 ± 1.6  | <0.001  |
| GMCSF (pg/ml)               | 1.9 ± 0.10 | 1.0 ± 0.11  | 0.003   |
| INF-gamma (pg/ml)           | 2.4 ± 0.74 | 1.6 ± 0.63  | 0.03    |
| IL4 (pg/ml)                 | 9.2 ± 1.4  | 18.5 ± 3.6  | 0.03    |
| IL5 (pg/ml)                 | 0.92 ± 0.20 | 0.52 ± 0.17 | <0.001  |
| IL8 (pg/ml)                 | 12.4 ± 1.8 | 6.3 ± 1.2  | 0.004    |
| IL10 (pg/ml)                | 12.1 ± 1.7 | 9.2 ± 1.4  | 0.03    |
| Naphthalene (ng/ml)         | 10.7 ± 2.7 | 26.2 ± 2.5 | <0.001   |
| Anthracene (ng/ml)          | 239.5 ± 22.6 | 260.1 ± 52.3 | 0.79    |
| Fluorene (ng/ml)            | 2.5 ± 0.75 | 3.6 ± 0.90  | 0.04    |
| Phenanthrene (ng/ml)        | 9.3 ± 1.7  | 11.5 ± 1.9  | 0.13    |
| 4H-cyclobenta[def]phenanthrene (ng/ml) | 6.2 ± 1.1  | 20.3 ± 2.1  | <0.001  |
| Pyrene (ng/ml)              | 0.67 ± 0.34 | 1.1 ± 0.50  | 0.04    |
| Fluoranthene (ng/ml)        | 26.9 ± 3.2 | 31.8 ± 3.4  | 0.60    |
| 1,2-benzanthracene (ng/ml)  | 0.37 ± 0.24 | 0.73 ± 0.36 | 0.01    |
| Chrysene (ng/ml)            | 0.87 ± 0.19 | 1.8 ± 0.13  | 0.001   |
| Benzo(a)pyrene (ng/ml)      | 1.6 ± 0.17 | 2.6 ± 0.20  | 0.32    |
| Benzo[a]pyrene (ng/ml)      | 1.7 ± 0.23 | 7.0 ± 0.90  | 0.006   |
| Benzo[al]pyrene (ng/ml)     | 2.1 ± 0.80 | 4.8 ± 0.93  | 0.02    |

To examine the role of PAHs in asthma, we analysed the association between PAHs and markers of asthma (Table 2). Our results clearly showed strong correlation between serum PAHs levels and asthma related biomarkers in Arab children. Thus, serum naphthalene was positively associated with IgE (r = 0.18, p = 0.03), IL-4 (r = 0.54, p = 0.001) and resistin (r = 0.19, p = 0.02) and negatively associated with IL-5 (r = -0.18, p = 0.03). 4H-cyclobenta[def]phenanthrene was positively associated with IgE (r = 0.18, p = 0.03), IL-4 (r = 0.54, p = 0.001) and negatively associated with IL-10 (r = -0.23, p = 0.02). 1,2-benzanthracene was positively associated with IgE (r = 0.27, p = 0.006), resistin (r = 0.34, p = 0.001) and negatively associated with IL-10 (r = -0.21, p = 0.03). Benzo
Mechanisms underlying the differences in PAHs levels may be multifactorial. These may be impacted by dietary preferences or lifestyle behaviors not measured in this study which might explain such changes. Additionally, genetic factors may impact on the metabolism of these compounds. Some of these possibilities have also been suggested by the NHANES report [20].

The present study showed positive associations between IgE and PAHs (naphthalene, 4H-cyclobenta[def] phenanthrene, 1,2-benzanthracene). The associations between PAHs levels and IgE levels reported in other studies indeed suggest that exposure to traffic-related air pollution results in an up-regulation of allergic immune responses [29-31]. In vitro studies have demonstrated that PAH-enhance IgE production via their effects on tensile B cells [32]. Exposure to pyrene has been associated with up-regulation of the IL-4 promoter [33]. In addition, different PAHs pyrene, benzo(a)-pyrene, anthracene, phenanthrene and fluoranthe has been shown to induce IgE production, T helper 2 cytokine productions in both rodent and studies highlighting the cellular impact of PAHs [34-36].

### Conclusion

Our results show that serum PAHs level is correlated with multiple asthma related biomarkers in children. Results herein also support the importance of Naphthalene, 4H-cyclobenta[def]phenanthrene, 1,2-benzanthracene, Chry-
sene and Benzo(e)acephenanthrylene in childhood asthma and clearly indicate that the plasma concentration of these compounds correlate with asthma related biomarkers including IgE, resistin, GMCSF, IFN-γ, IL-4, IL-5, IL-8 and IL-10.

### Abbreviations

PAHs: Polycyclic aromatic hydrocarbons; BMI: Body mass index; LDL: Low density lipoprotein; HDL: High density lipoprotein; SAD: Sagittal abdominal diameter.
Competing interests
The authors declared no competing interest with respect to the authorship and/or publication of this article.

Authors’ contributions
NMAD, MSA and SHAA designed and initiated the current study. NMAD, SHAA and MC were responsible for collecting the samples and the interview data. SHAA and HMD coordinated the current study. SHAA was responsible for the PAHs analysis using HPLC-FLD. HMD and SMY were responsible for the biochemical analyses. SHAA and HMD were responsible for writing the draft version of manuscript. NMAD, MSA, SMY and MC were responsible for reviewing the draft version of manuscript. All authors commented on and approved the final manuscript.

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