Internal exposure levels of polycyclic aromatic hydrocarbons in children and adolescents: a systematic review and meta-analysis

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Abstract

Polycyclic aromatic hydrocarbons (PAHs) are widely found in the environment, and comparing to adults, children are more vulnerable to PAHs exposure. Urinary metabolites of PAHs are used as preferred biomarkers to estimate the PAHs exposure. Systematic review on the internal exposure level of children and adolescents is rare. We aimed to calculate the internal exposure levels of PAHs in children and adolescents and compare the levels of PAHs internal exposure in various children groups. We searched PubMed, OVID, Web of Science, EBSCO, ACS, and four Chinese databases, and all studies examining the urinary concentrations of PAHs in children and adolescent were identified. The total exposure level of 11 PAHs metabolites were pooled. Standard mean difference (SMD) and 95% confidence intervals (CIs) of PAHs urinary concentration were calculated and pooled by RevMan5.3 to compare the exposure levels of different children groups. We found that 1-OHPyr, 2-OHNap, 2-OHFlu, 3-OHPhe, and 4-OHPhe were five PAHs metabolites most commonly studied in existing studies in children, and their total exposure levels were 0.38 ± 0.98, 2.32 ± 4.83, 0.81 ± 1.54, 0.09 ± 0.14, 0.03 ± 0.10 μmol/mol creatinine, respectively. The meta-analysis showed that the levels of 1-OHPyr were higher in higher environmental exposure group (SMD = 0.21, 95% CI = 0.03~0.40), ETS exposure group (SMD = 0.31, 95% CI = 0.08~0.54), and 6~11 years group (SMD = 0.16, 95% CI = 0.09~0.24); the level of 2-OHNap (SMD = 0.27, 95% CI = 0.01~0.53) was higher in higher environmental exposure group; however, the levels of 3-OHPhe (SMD = −0.34, 95% CI = −0.57~ −0.12) and 4-OHPhe (SMD = −0.48, 95% CI = −0.69~−0.28) were higher in lower environmental exposure group. The levels of 1-OHPyr (SMD = −0.01, 95% CI = −0.11~0.10) and 2-OHNap (SMD = 0.01, 95% CI = −0.20~0.22) were not statistically different between boys and girls. In conclusions, we found that the internal diversity of PAHs existed in children and adolescents, and the level of 1-OHPyr in children and adolescents was in higher status compared with non-occupational people who do not smoke.

Keywords: Polycyclic aromatic hydrocarbons, Children, Biological markers, Systematic review, Meta-analysis

Introduction

Polycyclic aromatic hydrocarbons (PAHs) are a group of over 100 different organic pollutants, which are widely found in the environment [1]. The major sources of PAHs are formed during the incomplete burning of coal, oil and gas, garbage, or other organic substances like tobacco or charbroiled meat [2]. Due to the numerous PAHs exposure sources, humans can be exposed to PAHs through multiple routes, including breathing polluted air, environmental tobacco smoke (ETS), dietary PAHs intake, and dermal absorption through soil, air, or particulate deposited on skin [3–5].

The exposure of PAHs in human has raised public health concerns. The United States Environmental Protection Agency (USEPA) has designated 16 PAH compounds as priority pollutants [3, 6]. Among PAHs, benzo[a]pyrene (BaP) has been classified as a probable human and animal carcinogen by the International Agency for Research on Cancer (IARC) [7, 8]. The exposure of PAHs has been
linked to the onset of diabetes mellitus [9], metabolic syndrome [10], and cardiovascular conditions [11]. Several studies reported that genotoxicity [12], oxidative stress [13], asthma [14], and neurodevelopment [15] were related to the exposure of PAHs. Besides, it has been found that PAHs exposure may be association with Cytochrome P450s (CYPs) induction and bioactivation, thereby leading to carcinogenesis [16]. Furthermore, existing studies showed that children are more vulnerable to PAHs exposure. Huang et al. reported that urinary 1-hydroxypyrene (1-OHPyr) concentration in children (6–11 years old) was approximately 30% higher compared to that in adults under the same conditions, indicating that children seem more susceptible to PAHs and have higher potential health risks [50].

Compared to monitoring of the external environment (e.g., measurement of chemicals in air, water, or soil), human biomonitoring reflects internal exposure in the human through different routes of exposure [17]. After entering the human body and biotransformation, PAHs are excreted in the form of hydroxylated metabolites in the urine or stool [18]. Biomarkers can provide an integrated reflection for exposure through inhalation, food and dermal uptake, and takes into account variation in absorption, metabolism, and elimination by the body. Therefore, the urinary metabolites of these compounds are used as preferred biomarkers to estimate the PAHs exposure [19].

To date, a number of studies have detected the urinary metabolites concentration of PAHs; however, the biomarkers and characteristics were diverse. Several studies conducted a review on the concentration of urinary metabolites and biomarkers of PAHs. A comprehensive review on occupational exposure to PAHs by Bouchard et al. [20] revealed that urinary 1-OHPyr increased in course of a working day. Hansen et al. [21] reviewed 132 studies addressing the use of 1-OHPyr as a biomarker of both occupational and environmental exposure to PAH. Of these, 25 studies addressed environmental exposure, and only nine included children. The existing reviews on PAHs metabolites concentration are focused more on adults, but comprehensive review on the internal exposure level of children and adolescence is rare. The purpose of this study was to estimate the total non-occupational internal exposure level in children using different hydroxylated metabolites and to compare the levels of PAHs internal exposure in various children groups. Furthermore, a reference for future research and evaluation on PAHs biomarkers in children will be provided from the estimated total internal exposure level.

**Methods**

**Selection criteria**

The inclusion criteria included (1) studies that reported the urinary concentrations of PAHs metabolites; (2) participants: children and adolescents whose age under 20 years; and (3) outcome: concentration of PAHs hydroxylated metabolites (the preferred indicators were mean and standard deviation, median and range were included after calculating by formula). We excluded studies if (1) the studies were reviews, editorials, meeting abstracts, or commentaries; and (2) the small sample size studies detected concentration of PAHs to verify the feasibility of detection method. We did not have language restrictions.

**Search strategy**

The databases including PubMed (1978 to January 2017), OVID (1946 to January 2017), Web of Science (1970 to January 2017), EBSCO (1976 to January 2017), ACS(1879 to January 2017), CNKI (1979 to January 2017), WANFANG DATA (1987 to January 2017), CBM (1978 to January 2017), and CQVIP (1989 to January 2017) were searched using both the MeSH terms and free terms “Polycyclic Aromatic Hydrocarbons” or “PAHs” or “hydroxypyrene” or “hydroxyfluorene” or “hydroxyphenanthrene” or “hydroxynaphthalene” or “hydroxyfluoranthene” or “hydroxybenzo[c]phenanthrene” or “hydroxychrysene” or “hydroxybenz[a]anthracene,” in combination with “urinary.” We modified the search strategy when searching in different databases. No language restrictions or restrictions on publication type were applied. All the retrieved literatures were entered into reference-managing software (EndNote, version X6, Thomson Scientific, Stamford, CT, USA) for duplicate check.

**Data screening and extraction**

Two reviewers independently screened all the retrieved literature by titles and abstracts. The potential eligible studies were then screened again by full texts. The pre-designed criteria mentioned above were used to guide the entire process of screening. Subsequently, the following data were extracted from all the included studies using a pre-designed extraction form by two reviewers: (1) general information, including authors, publication year, country; (2) study design and methodological quality; (3) participants characteristics and sample size; (4) sample collection season; (5) analyte detection and adjusted methods; and (6) outcome measures, including type of metabolites, outcome indicators, and concentrations of metabolites. Disagreements during screening and data extraction were resolved by discussion or consultation with the third reviewer to reach a consensus.

**Risk of bias assessment**

Two reviewers independently assessed the methodology quality of included studies using the checklist recommended by Agency for Healthcare Research and Quality (AHRQ) [22]. Every item should be answered by “Yes,”
"No," or “Unclear.” Disagreements were resolved by discussion or consultation with the third reviewer to reach a consensus.

Recalculation of urinary PAHs
The given concentrations were recalculation where the concentrations were given in the unit of ng/g creatinine, ng/mg creatinine, and nmol/mol creatinine. For the recalculation molecular weight of hydroxypyrene (218.25), hydroxynaphthalene (144.17), hydroxyfluorene (182.22), hydroxyphenanthrene (194.23), and creatinine (113.12) were used. Outcome reported with median and ranges or median and interquartile range were converted to means and standard deviations according to the formula for approximately estimating [23, 24].

Statistical analysis
A statistical formula (Fig. 1) was used to synthesize means and standard deviations to get a total level of PAHs metabolites. The standard mean difference (SMD) and 95% confidence interval (95% CI) of concentrations of PAHs metabolites were used to conduct meta-analyses using the software of Review Manager Software (Version 5.3, Cochrane Collaboration, London, UK) for comparison between different children groups. The statistical heterogeneity of the included studies was assessed by \( \chi^2 \) test and \( I^2 \) index. A random effects model was used when heterogeneity was found to be significant (\( I^2 > 50\% \) or \( P < 0.05 \)); otherwise, the fixed effects model was used. Sensitivity analyses were conducted using the leave-one-out approach for all the outcomes. To examine the potential publication bias, we used the funnel plot firstly. When larger and smaller studies were non-symmetrically distributed, visual inspection of the funnel plot offered an indication of publication bias. The presence of publication bias was further tested using Begg’s test and Egger’s test by STATA 12.0 software (StataCorp LP, College Station, TX). A \( P \leq 0.05 \) was considered to be statistically significant.

Results
Screening results
The process of study selection is shown in Fig. 2 with an adapted PRISMA (Preferred reporting items for systematic reviews and meta-analyses) flow diagram [25]. A total of 4776 records were identified after searching the literature. After duplicate checking, 2984 studies were excluded after the initial screening of titles and abstracts. Forty studies described in 42 articles [26–67] involving 12697 subjects were included in the final review after a strict screening process based on eligibility criteria, of which, 26 studies [26–53, 66] were included in the meta-analysis. The other 315 studies were excluded because they did not report the concentration of PAHs, or were not relevant to children and adolescent, or duplicate publication or studies were reviews, meeting abstracts, or commentaries.

Characteristics of included studies
Table 1 presents the main characteristics of included studies. The earliest study began in 1993. Seventeen [27, 28, 30–32, 38, 41–43, 47, 50, 52, 53, 56, 59, 60, 64, 67] of 40 studies were performed in developed countries or regions, and 23 [26, 29, 33–37, 39, 40, 44–46, 48, 49, 51, 54, 55, 57, 58, 61–63, 65, 66] were conducted in developing countries. A total of 12697 children were enrolled in this review, of which age range were 0–20 years. Six studies [39, 46, 48, 61, 63, 64] did not mentioned the age of subjects, but they reported that the subjects were all the elementary school students. Six studies [45, 48, 54, 55, 59, 62] detected the level of PAHs metabolites only in boys, the remaining [26–29, 33–49, 51, 53–55, 57–67] included both girls and boys. Five out of 40 studies [30–32, 50, 52, 56] determined the PAHs metabolites by gas chromatography (GC), the remaining [26–29, 33–49, 51, 53–55, 57–67] used the high-performance liquid chromatography (HPLC) method. The numbers of metabolites were from one to 11, and all the studies reported concentration of 1-OHPyr. Of the 42 articles based on the 40 studies, 29 [26, 28, 29, 32–34, 36, 38–44, 46, 48, 49, 53–64] reported the level of PAHs by mean and standard deviation, five [30, 31, 50–52] reported by mean and its 95% CI, three [27, 45, 67]

![Table 1](Fig. 1) Formula of combination
reported by mean and range, three [47, 65, 66] reported by median and range, and two [35, 37] reported by median and interquartile range. Thirty-seven of 40 studies reported the PAHs metabolites concentrations adjusted by creatinine, one study in two papers [30, 31] reported the concentrations adjusted by urine specific gravity (SG), and two studies [51, 64] reported the unadjusted concentrations. Sixteen studies compared the urine PAHs metabolites levels between children living in higher PAHs exposure environment and lower exposure environment. The higher living environment included the urban areas [27, 32, 38, 41, 45], industrial city or areas [40, 46, 48, 49], commercial areas [39], and schools or communities close to main roads [44], steel plant [43], steel mill and coking facility [33], power plant [42], coke oven plant [47], or oil refinery [37]. Oppositely, the rural areas [27, 32, 38, 41, 45, 47], tourist city [40], agricultural or residential areas [46, 48, 49], and schools or communities far away from the industry plants [33, 37, 42–44] were regarded as the lower living environment.

**Risk of bias in included studies**

The quality assessment of cross-sectional studies was shown in Table 2. Of the 11 items in quality assessment, all the studies reported the data sources, inclusion and exclusion criteria for exposed and unexposed subjects, study period, and all the subjects were consecutive; it is unclear in all studies that whether or not the evaluators of subjective components were masked to other aspects of the status of the participants; only two studies [51, 64] did not adjust the levels of PAHs; five studies [30, 31, 33, 42, 43, 45] described the reasons for sample exclusions from analysis; 15 studies [34, 40, 44, 46–49, 56–58, 60, 63, 65–67] did not describe how to control confounding factors; only two studies [43, 45] explained how to deal with the data below the limit of detection; 11 studies [27, 33, 35–37, 42, 43, 45, 47, 50, 51, 60] described the completeness of data collection; and four studies [26, 30, 31, 43, 48] had follow-ups and reported the percentage of patients obtained in follow-ups.

**Total exposure levels of PAHs**

In this study, the concentration of 11 PAHs metabolites in urine of children and adolescents were pooled based on the 37 studies [26–29, 32–50, 52–63, 65–67] reporting the concentrations adjusted by creatinine respectively. 1-OHPyr, 2-OHNap, 2-OHFlu, 3-OHPhe, and 4-OHPhe were five PAHs metabolites most commonly used in existing studies, and their total exposure levels were 0.38 ± 0.98, 2.32 ± 4.83, 0.81 ± 1.54, 0.09 ± 0.14 and 0.03 ± 0.10 μmol/mol creatinine, respectively. Among three age groups, the concentration of 9-OHPhe (1.90 ± 1.20) in children under six were higher than those in other age groups; the concentration of 1-OHPyr (0.45 ± 0.75) in children aged 6 to 11 years was higher than that in other groups. Between the age groups of 6 to 11 years and 12 to 20 years, the concentration of 1-OHNap (1.95 ± 2.56), 2-OHNap (2.37 ± 5.34), 3-OHFlu (0.09 ± 0.22), and 9-OHFlu (0.15 ± 0.36) in adolescent aged 12 to 20 years were higher than those in six to 11 years group; the concentration of 2-OHFlu (1.48 ± 0.20), 1-OHPhe (0.09 ± 0.17), 2-OHPhe (0.07 ± 0.19), 3-OHPhe (0.14 ± 0.20), and 4-OHPhe (0.04 ± 0.15) in children aged 6 to 11 years.
| Study | Country/Areas | Study period | Sample size (Boys/Girls) | Age range | Sample collection season | Analyte detection | Adjusted methods | Metabolites | Outcome indicators |
|-------|---------------|--------------|--------------------------|-----------|--------------------------|-------------------|-----------------|-------------|-------------------|
| Chen 2015 [26] | Mongolia | 2011–2012 | 320 (166/154) | 11–15 years | Spring, autumn, winter | HPLC-FD | Creatinine | 1-OHPyr | Mean ± SD |
| Hansen 2005 [27] | Denmark | 1994–1995 | 204 (108/96) | 7–8 years | Winter | HPLC-FD | Creatinine | 1-OHPyr | Mean (range) |
| Kang 2002 [28] | Korea | 1997 | 137 (78/59) | 11–14 years | Summer | HPLC-FD | Creatinine | 1-OHPyr, 2-OHNap | Mean ± SD |
| Melnykova 2006 [29] | Poland | 1998–1999 | 74 (47/27) | 5–14 years | Winter | HPLC-FD | Creatinine | 1-OHPyr | Mean ± SD |
| Miller 2010 [30] | USA | 1998–2006 | 222 (119/103) | 5 years | Irregular | GC-MS/MS | 5G | 1-OHPyr, 1-OHNap, 2-OHNap, 2-OHFlu, 3-OHFlu, 9-OHFlu, 1-OHPhe, 2-OHPhe, 3-OHPhe, 4-OHPhe | Mean (95% CI) |
| Jung 2015 [31] | USA | 2000–2001 | 126 (63/63) | 2–years | Spring, summer, autumn | GC/MS | Creatinine | 1-OHPyr | Mean ± SD |
| Mucha 2006 [32] | Ukraine | 1998 | 90 (43/47) | 3 years | Spring | HPLC | Creatinine | 1-OHPyr | Mean ± SD |
| Ochoa-Martinez 2016 [33] | Mexico | 2012 | 135 (NA) | 6–12 years | Not mentioned | HPLC-FD | Creatinine | 1-OHPyr | Mean ± SD |
| Yue 2010(1) [34] | China | 2007 | 80 (47/33) | 4–6 years | Winter | HPLC-FD | Creatinine | 1-OHPyr | Mean ± SD |
| Yue 2011 [35] | USA | 2000–2001 | 170 (NA) | 11 years | Spring | HPLC | Creatinine | 1-OHPyr, 3-OHFlu, 1-OHPhe, 2-OHPhe, 3-OHPhe, 4-OHPhe, 9-OHPhe | Mean (95% CI) |
| Alghamdi 2015 [36] | Saudi Arabian | 2013 | 170 (NA) | 11 years | Spring | HPLC | Creatinine | 1-OHPyr, 3-OHFlu, 1-OHPhe, 2-OHPhe, 3-OHPhe, 4-OHPhe | Mean (interquartile range) |
| Cirillo 2006 [37] | Italian | 2004 | 30 (15/15) | 7–9 years | Winter | HPLC-UV | Creatinine | 1-OHPyr | Mean ± SD |
| Duan 2003 [38] | China | 2002 | 40 (NA) | Not mentioned | Winter | HPLC | Creatinine | 1-OHPyr | Mean ± SD |
| Fan 2007 [39] | China | 2005 | 108 (72/36) | 16–18 years | Spring, summer | HPLC-MS/MS | Creatinine | 1-OHPyr, 1-OHNap, 2-OHNap, 2-OHFlu, 2-OHPhe, 3-OHPhe, 4-OHPhe, 9-OHPhe | Mean ± SD |
| Freire 2009 [40] | Spain | 2005–2006 | 174 (NA) | 4 years | Irregular | HPLC | Creatinine | 1-OHPyr | Mean ± SD |
| Hu 2011 [41] | Taiwan/China | 2009 | 369 (198/171) | 1–13 years | Autumn, winter | HPLC | Creatinine | 1-OHPyr | Mean ± SD |
| Lee 2007 [42] | Korea | 2004 | 1012 (475/537) | 7–15 years | Spring | HPLC | Creatinine | 1-OHPyr | Mean ± SD |
| Ruchirawat 2007 [43] | Thailand | 2006 | 176 (NA) | 9–13 years | Not mentioned | HPLC | Creatinine | 1-OHPyr | Mean ± SD |
| Shahsavani 2016 [44] | Iran | 2015 | 120 (120/0) | 9–12 years | Spring | HPLC | Creatinine | 1-OHPyr | Mean (range) |
| Su 2015 [45] | China | 2014 | 164 (NA) | Not mentioned | Autumn | HPLC-MS | Creatinine | 1-OHPyr, 1-OHNap, 2-OHNap, 2-OHFlu, 3-OHFlu, 1-OHPhe, 2-OHPhe, 3-OHPhe, 4-OHPhe, 9-OHPhe | Mean ± SD |
| Wilhelm 2007 [46] | Germany | 2000 | 215 (NA) | 4–9 years | Spring | HPLC | Creatinine | 1-OHPyr | Mean (range) |
| Yang 1997 [47] | China | 1994 | 88 (88/0) | Not mentioned | Summer, winter | HPLC | Creatinine | 1-OHPyr | Mean ± SD |
| Yu 2012 [48] | China | 2010–2011 | 185 (NA) | 9–12 years | Winter | HPLC | Creatinine | 1-OHPyr | Mean ± SD |
| Huang 2006 [49] | USA | 1999–2000 | 1003 (NA) | 6–19 years | Not mentioned | GC/IDHRMS | Creatinine | 1-OHPyr | Mean (95% CI) |
| Study | Country/Areas | Study period | Sample size (Boys/Girls) | Age range | Sample collection season | Analyte detection | Adjusted methods | Metabolites | Outcome indicators |
|-------|---------------|--------------|--------------------------|-----------|--------------------------|------------------|-----------------|-------------|-------------------|
| Huang 2014 [51] | China | 2009–2010 | 2015 (NA) | 6–20 years | Not mentioned | HPLC | Unadjusted | 1-OHPyr, 1-OHNap, 2-OHNap, 3-OHPhe | Mean (95%CI) |
| Li 2008 [52] | USA | 2001–2002 | 1122 (NA) | 6–19 years | Not mentioned | GC/IDHRMS | Creatinine | 1-OHPyr, 1-OHNap, 2-OHNap, 2-OHFlu, 3-OHFlu, 9-OHFlu, 1-OHPhe, 2-OHPhe, 3-OHPhe, 4-OHPhe, 9-OHPhe | Mean (95% CI) |
| Heudorf 2001 [53] | Germany | 1998 | 718 (NA) | 0–20 years | Spring | HPLC-FD | Creatinine | 1-OHPyr, 1-OHPhe, 2-OHPhe, 3-OHPhe, 4-OHPhe | Mean ± SD |
| Yue 2010(2) [54] | China | 2006 | 15 (15/0) | 14–18 years | Winter | HPLC-FD | Creatinine | 1-OHPyr, 2-OHNap, 2-OHFlu, 2-OHPhe, 3-OHPhe, 4-OHPhe, 9-OHPhe | Mean ± SD |
| Yue 2009 [55] | China | 2005 | 41 (41/0) | 16–18 years | Summer | HPLC-FD | Creatinine | 1-OHPyr, 2-OHNap, 2-OHFlu, 2-OHPhe, 3-OHPhe, 4-OHPhe, 9-OHPhe | Mean ± SD |
| Farzan 2016 [56] | USA | 2003–2008 | 660 (NA) | 12–19 years | Not mentioned | GC/IDHRMS | Creatinine | 1-OHPyr, 1-OHNap, 2-OHNap, 2-OHFlu, 3-OHFlu, 9-OHFlu, 1-OHPhe, 2-OHPhe, 3-OHPhe, 4-OHPhe | Mean ± SD |
| Perez -Maldonado 2014 [57] | Mexico | 2008–2009 | 226 (112/114) | 6–12 years | Not mentioned | HPLC | Creatinine | 1-OHPyr | Mean ± SD |
| Martinez -Salinas 2010 [58] | Mexico | 2010 | 258 (NA) | 3–13 years | Not mentioned | HPLC | Creatinine | 1-OHPyr | Mean ± SD |
| Cavanagh 2007 [59] | New Zealand | 2004 | 89 (89/0) | 12–18 years | Autumn, winter | HPLC | Creatinine | 1-OHPyr | Mean ± SD |
| Wijnen 1996 [60] | The Netherlands | 1992 | 644 (NA) | 1–6 years | Summer | HPLC-FD | Creatinine | 1-OHPyr | Mean ± SD |
| Ma 1996 [61] | China | 1992–1994 | 574 (NA) | Not mentioned | Summer, winter | HPLC-FD | Creatinine | 1-OHPyr | Mean ± SD |
| Zhao 1995 [62] | China | 1991–1992 | 310 (310/0) | 6–15 years | Spring, autumn, winter | HPLC | Creatinine | 1-OHPyr | Mean ± SD |
| Ma 1994 [63] | China | 1992 | 145 (NA) | Not mentioned | Autumn, winter | HPLC | Creatinine | 1-OHPyr | Mean ± SD |
| Kanoh 1993 [64] | Japan | 1988–1989 | 139 (NA) | Not mentioned | Summer, winter | HPLC | Unadjusted | 1-OHPyr | Mean ± SD |
| Swirńska 1998 [65] | Poland | 1996 | 30 (18/12) | 8 years | Not mentioned | HPLC | Creatinine | 1-OHPyr | Median (range) |
| Swirńska 1999 [66] | Poland | 1996 | 412 (NA) | 7–8 years | Not mentioned | HPLC | Creatinine | 1-OHPyr | Median (range) |
| Fiala 2001 [67] | The Czech Republic | 1997–1998 | 57 (NA) | 3–6 years | Summer, winter | HPLC-FD | Creatinine | 1-OHPyr | Mean (range) |

OH Pyr hydroxypyrene, OHNap hydroxynaphalene, OHFlu hydroxyfluorene, OHPhe hydroxyphenanthrene, HPLC high-performance liquid chromatography, FD fluorescence detection, UV ultraviolet, MS mass spectrometry, GC gas chromatography, IDHRMS isotope dilution high-resolution mass spectrometry, SG specific gravity, SD standard deviation, NA not available.
| Study                  | (1) | (2) | (3) | (4) | (5) | (6) | (7) | (8) | (9) | (10) | (11) |
|-----------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|------|
| Chen 2015 [26]        | Y   | Y   | Y   | Y   | U   | Y   | N   | Y   | N   | N    | Y    |
| Hansen 2005 [27]      | Y   | Y   | Y   | Y   | U   | Y   | N   | Y   | N   | Y    | N    |
| Kang 2002 [28]        | Y   | Y   | Y   | Y   | U   | Y   | N   | Y   | N   | N    | N    |
| Mielzynska 2006 [29]  | Y   | Y   | Y   | Y   | U   | Y   | N   | Y   | N   | N    | N    |
| Miller 2010 [30]      | Y   | Y   | Y   | Y   | U   | Y   | Y   | Y   | N   | Y    | Y    |
| Jung 2015 [31]        |     |     |     |     |     |     |     |     |     |      |      |
| Morgan 2015 [32]      | Y   | Y   | Y   | Y   | U   | Y   | N   | Y   | N   | N    | N    |
| Mucha 2006 [33]       | Y   | Y   | Y   | Y   | U   | Y   | N   | Y   | N   | N    | N    |
| Ochoa-Martinez 2016 [34] | Y   | Y   | Y   | Y   | U   | Y   | N   | N   | N   | N    | N    |
| Yue 2010(1) [35]      | Y   | Y   | Y   | Y   | U   | Y   | N   | Y   | N   | Y    | N    |
| Yue 2011 [36]         |     |     |     |     |     |     |     |     |     |      |      |
| Alghamdi 2015 [37]    | Y   | Y   | Y   | Y   | U   | Y   | N   | Y   | N   | N    | N    |
| Cirillo 2006 [38]     | Y   | Y   | Y   | Y   | U   | Y   | N   | Y   | N   | N    | N    |
| Duan 2003 [39]        | Y   | Y   | Y   | Y   | U   | Y   | N   | Y   | N   | N    | N    |
| Fan 2007 [40]         | Y   | Y   | Y   | Y   | U   | Y   | N   | N   | N   | N    | N    |
| Freire 2009 [41]      | Y   | Y   | Y   | Y   | U   | Y   | N   | Y   | N   | N    | N    |
| Hu 2011 [42]          | Y   | Y   | Y   | Y   | U   | Y   | Y   | Y   | N   | Y    | N    |
| Lee 2007 [43]         | Y   | Y   | Y   | Y   | U   | Y   | Y   | Y   | Y   | Y    | N    |
| Ruchirawat 2007 [44]  | Y   | Y   | Y   | Y   | U   | Y   | N   | N   | N   | N    | N    |
| Shahsavani 2016 [45]  | Y   | Y   | Y   | Y   | U   | Y   | Y   | Y   | Y   | Y    | N    |
| Su 2015 [46]          | Y   | Y   | Y   | Y   | U   | Y   | N   | N   | N   | N    | N    |
| Wilhelm 2007 [47]     | Y   | Y   | Y   | Y   | U   | Y   | N   | N   | N   | Y    | N    |
| Yang 1997 [48]        | Y   | Y   | Y   | Y   | U   | Y   | N   | N   | N   | N    | Y    |
| Yu 2012 [49]          | Y   | Y   | Y   | Y   | U   | Y   | N   | N   | N   | N    | N    |
| Huang 2006 [50]       | Y   | Y   | Y   | Y   | U   | Y   | N   | Y   | N   | Y    | N    |
| Huang 2014 [51]       | Y   | Y   | Y   | Y   | U   | N   | N   | Y   | N   | Y    | N    |
| Li 2008 [52]          | Y   | Y   | Y   | Y   | U   | Y   | N   | Y   | N   | N    | N    |
| Heudorf 2001 [53]     | Y   | Y   | Y   | Y   | U   | Y   | N   | Y   | N   | N    | N    |
| Yue 2010(2) [54]      | Y   | Y   | Y   | Y   | U   | Y   | N   | Y   | N   | N    | N    |
| Yue 2009 [55]         | Y   | Y   | Y   | Y   | U   | Y   | N   | Y   | N   | N    | N    |
| Farzan 2016 [56]      | Y   | Y   | Y   | Y   | U   | Y   | N   | N   | N   | N    | N    |
| Perez-Maldonado 2014 [57] | Y   | Y   | Y   | Y   | U   | Y   | N   | N   | N   | N    | N    |
| Martinez-Salinas 2010 [58] | Y   | Y   | Y   | Y   | U   | Y   | N   | N   | N   | N    | N    |
| Cavanagh 2007 [59]    | Y   | Y   | Y   | Y   | U   | Y   | N   | Y   | N   | N    | N    |
| Wijnen 1996 [60]      | Y   | Y   | Y   | Y   | U   | Y   | N   | N   | N   | Y    | N    |
| Ma 1996 [61]          | Y   | Y   | Y   | Y   | U   | Y   | N   | Y   | N   | N    | N    |
| Zhao 1995 [62]        | Y   | Y   | Y   | Y   | U   | Y   | N   | Y   | N   | N    | N    |
| Ma 1994 [63]          | Y   | Y   | Y   | Y   | U   | Y   | N   | N   | N   | N    | N    |
| Kanoh 1993 [64]       | Y   | Y   | Y   | Y   | U   | N   | N   | Y   | N   | N    | N    |
| Siwińska 1998 [65]    | Y   | Y   | Y   | Y   | U   | Y   | N   | N   | N   | N    | N    |
| Siwińska 1999 [66]    | Y   | Y   | Y   | Y   | U   | Y   | N   | N   | N   | N    | N    |
| Fiala 2001 [67]       | Y   | Y   | Y   | Y   | U   | Y   | N   | N   | N   | N    | N    |

(1) Define the source of information (survey, record review); (2) list inclusion and exclusion criteria for exposed and unexposed subjects (cases and controls) or refer to previous publications; (3) indicate time period used for identifying patients; (4) indicate whether or not subjects were consecutive if not population-based; (5) indicate if evaluators of subjective components of study were masked to other aspects of the status of the participants; (6) describe any assessments undertaken for quality assurance purposes (e.g., test/retest of primary outcome measurements); (7) explain any patient exclusions from analysis; (8) describe how confounding was assessed and/or controlled; (9) if applicable, explain how missing data were handled in the analysis; (10) summarize patient response rates and completeness of data collection; (11) clarify what follow-up, if any, was expected and the percentage of patients for which incomplete data or follow-up was obtained. Y yes, N no, U unclear
were higher than those in 12 to 20 years age groups. Details are shown in Table 3.

**Comparison of PAHs metabolites levels in various children groups**

**1-OHPyr**

Living environment and 1-OHPyr levels Meta-analysis based on 16 studies [27, 32, 33, 37–49] indicated that the level of 1-OHPyr was higher in children living with higher environmental exposure than that in children living with lower exposure (SMD = 0.21, 95% CI = 0.03–0.40) (Fig. 3). A random effects model was adopted (P < 0.05, I² = 82%). Subgroup analyses by countries, ages, gender, type of data, study period, and sample collection seasons are shown in Table 4. Statistical differences in levels of 1-OHPyr between higher exposure group and lower exposure group were found in subgroups of developing countries (SMD = 0.37, 95% CI = 0.03–0.72), both genders (SMD = 0.25, 95% CI = 0.04–0.46), and study period in 2001–2010 (SMD = 0.27, 95% CI = 0.04–0.50).

Environmental tobacco smoke and 1-OHPyr levels Meta-analysis based on six studies [29, 32, 35, 41, 45, 66] indicated that the level of 1-OHPyr was higher in children exposed to ETS than that in children not exposed to ETS (SMD = 0.31, 95% CI = 0.08–0.54) (Fig. 4). A random effects model was adopted (P < 0.05, I² = 59%). The pooled results were not changed in each individual sensitivity analysis by the leaving one out approach.

**Table 3** Concentration of 11 PAHs metabolites in children and adolescents

| Metabolites | No. of studies | Concentrations in different age groups (Mean ± SD, μmol/mol Cre.) |
|-------------|----------------|---------------------------------------------------------------|
|             |                | < 6 years | 6–11 years | 12–20 years | Total           |
| 1-OHPyr     | 37             | 0.24 ± 0.35 | 0.45 ± 0.75 | 0.18 ± 0.52 | 0.38 ± 0.98     |
| 1-OHNap     | 4              | –         | 1.78 ± 3.07 | 1.95 ± 2.56 | 1.90 ± 2.78     |
| 2-OHNap     | 7              | –         | 2.18 ± 2.67 | 2.37 ± 3.34 | 2.32 ± 4.83     |
| 2-OHFlu     | 6              | –         | 1.48 ± 0.20 | 0.38 ± 1.38 | 0.81 ± 1.54     |
| 3-OHFlu     | 2              | –         | 0.07 ± 0.19 | 0.09 ± 0.22 | 0.08 ± 0.21     |
| 9-OHFlu     | 2              | –         | 0.11 ± 0.20 | 0.15 ± 0.36 | 0.14 ± 0.33     |
| 1-OHPhe     | 3              | –         | 0.09 ± 0.17 | 0.07 ± 0.11 | 0.08 ± 0.13     |
| 2-OHPhe     | 4              | –         | 0.07 ± 0.19 | 0.06 ± 0.07 | 0.07 ± 0.12     |
| 3-OHPhe     | 5              | –         | 0.14 ± 0.20 | 0.07 ± 0.10 | 0.09 ± 0.14     |
| 4-OHPhe     | 8              | –         | 0.04 ± 0.15 | 0.02 ± 0.05 | 0.03 ± 0.10     |
| 9-OHFlu     | 4              | 1.90 ± 1.20 | 0.02 ± 0.02 | 0.16 ± 0.45 | 0.29 ± 0.76     |

The concentration of 2-OHNap, 1-OHNap, 2-OHFlu, 3-OHFlu, 9-OHFlu, 1-OHPhe, 2-OHPhe, 3-OHPhe, and 4-OHPhe in children aged under 6 years were not pooled due to the lack of data.

**Fig. 3** Meta-analysis on differences of level of 1-OHPyr in children and adolescents with different living condition
Gender and 1-OHPyr levels Meta-analysis based on 1549 subjects [26–35] indicated that the level of 1-OHPyr in girls were higher than that in boys (SMD = -0.72, 95% CI = -1.28--0.15) (Fig. 5). A random effects model was adopted (P < 0.05, I² = 96%). However, after removing Kang 2002 [28] in sensitivity analysis, the pooled data changed to no statistical difference between genders (SMD = -0.01, 95% CI = -0.11--0.10), and the heterogeneity reduced to 0% (Fig. 6).

Age and 1-OHPyr levels Four studies [50–53] pooled the data of 1-OHPyr in different age group, showing that the concentration of 1-OHPyr in the 6–11 years group was higher than that in 12–19 years group (SMD = 0.16, 95% CI = 0.09–0.23), (Fig. 7). The fixed effects model was adopted (P > 0.05, I² = 0%).

2-OHNap

Living environment and 2-OHNap levels Two studies [40, 46] reported the concentration of 2-OHNap. The pooled data showed that the concentration of 2-OHNap detected in children living with higher PAHs exposure was higher than that in children with lower exposure (SMD = 0.27, 95% CI = 0.01--0.53); the fixed effects model was adopted (P > 0.05, I² = 35%), (Fig. 8).

Gender and 2-OHNap levels Two studies [28, 30] pooled the data of concentration of 2-OHNap, showing that there were no statistical differences in the level of 2-OHNap between boys and girls (SMD = 0.01, 95% CI = -0.20--0.22); the fixed effects model was adopted (P > 0.05, I² = 0%), (Fig. 9).

Other metabolites

Two studies [40, 46] pooled the data of 1-OHNap and 2-OHPhe, and three studies [37, 40, 46] pooled the data of 3-OHPhe and 4-OHPhe. The pooled data showed no significant differences in urinary concentration of 1-OHNap, 2-OHPhe and 3-OHPhe between the groups living with higher/lower environmental exposure (Table 5).
while the concentration of 4-OHPhe detected in children living with lower exposure was higher than that in children with higher exposure (SMD = -0.48, 95% CI = -0.69--0.28, Additional file 1: Figure S11).

When the data of Fan 2007 [40] were removed in sensitivity analysis of 3-OHPhe, the pooled result altered (SMD = -0.34, 95%CI = -0.57--0.12), and the heterogeneity reduced to 0% (Additional file 1: Figure S10).

**Discussion**

PAHs are widely diffused in the environment, and there is a high risk for human to expose to it. Knowing the exposure level of PAHs and comparing the levels in various groups can provide basic data for the environment pollution control, and can also contribute to the further study on association of PAHs with human health. A total of 12697 children were enrolled in this study, covering 19 countries or areas of five continents, detecting 11 kinds of PAHs urinary metabolites. To the best of our knowledge, this is the first systematic review and meta-analysis to estimate the total level of non-occupational internal exposure of PAHs and to compare exposure levels of PAHs metabolites in various groups of children and adolescents.

The present study pooled the total concentration of 11 PAHs metabolites in children and adolescents based on 37 studies including 10321 children. 1-OHPyr is the most widely used biomarker of PAHs, and several [68–70] studies reported the occupational exposure limit (OEL) of 1-OHPyr. However, there is lack of the limit value for general population, nor for children. Jongeneelen et al. [68] suggested that the reference value in non-occupational people is 0.24 μmol/mol creatinine and 0.76 μmol/mol creatinine for non-smokers and smokers, respectively; however, the pooled value of 1-OHPyr in children in this study was 0.38 μmol/mol creatinine, which is higher than the reference value. 1-OHNap and 2-OHNap were the highest levels of PAHs metabolites in the urine of children, with the pooled value of 1.90 and 2.32 μmol/mol creatinine, respectively.

Except for 1-OHPyr, all the other ten PAHs biomarkers have no reference or limit value; the pooled concentration in this study could provide a reference for future research and evaluation on PAHs.

**Table 1**

| Study or Subgroup | Boys | Girls | Std. Mean Difference | Std. Mean Difference |
|-------------------|------|-------|----------------------|----------------------|
| Mean | SD | Total | Mean | SD | Total | Weight | N. Random, 95% CI | N. Random, 95% CI |
|--------|---------|-----------------|--------|---------|-----------------|-----------------|-----------------|-----------------|
| Chen 2015 | 0.29 | 0.53 | 166 | 0.32 | 0.6 | 154 | 22.9% | -0.05 [-0.27, 0.17] |
| Hansen 2005(1) | 0.13 | 0.13 | 55 | 0.12 | 0.155 | 45 | 7.1% | 0.07 [0.32, 0.46] |
| Hansen 2005(2) | 0.17 | 0.4125 | 51 | 0.1 | 0.1325 | 46 | 9.5% | 0.22 [-0.18, 0.62] |
| Kang 2002 | 83.1 | 3.94 | 78 | 122.73 | 2.83 | 59 | 6.2% | -11.24 [12.83, -9.65] |
| Mielzynska 2006 | 0.51 | 0.29 | 47 | 0.56 | 0.35 | 27 | 4.9% | -0.22 [-0.70, 0.26] |
| Miller 2010 | 141 | 153.06 | 119 | 143 | 126.86 | 103 | 15.8% | -0.01 [-0.28, 0.25] |
| Morgan 2015 | 0.33 | 0.03 | 63 | 0.32 | 0.0225 | 63 | 8.9% | 0.37 [0.02, 0.73] |
| Mucha 2006(1) | 0.31 | 0.21 | 18 | 0.37 | 0.19 | 23 | 2.9% | -0.30 [-0.92, 0.32] |
| Mucha 2006(2) | 0.62 | 0.45 | 16 | 0.74 | 0.53 | 16 | 2.3% | -0.24 [-0.93, 0.46] |
| Ochoa-Martinez 2016 | 0.13 | 0.2 | 106 | 0.15 | 0.23 | 154 | 22.9% | -0.09 [-0.31, 0.13] |
| Yue 2010(1) | 0.37 | 0.29 | 47 | 0.38 | 0.16 | 33 | 9.3% | -0.94 [-0.49, 0.40] |

Total (95% CI): 748

**Fig. 5** Meta-analysis on differences of level of 1-OHPyr in children and adolescents by gender

**Fig. 6** Sensitivity analysis of meta-analysis on differences of level of 1-OHPyr in children and adolescents by gender
biomarkers in children. Compared to the general population, the levels of 1-OHPyr and 3-OHPhe in this study were higher than those in the USA [56] and lower than those in China [51]. Contrarily, the levels of 1-OHNap and 2-OHNap were higher than those in China [51] and lower than those in the USA [56].

This study found that level of 1-OHPyr in children living with higher environmental exposure was higher than that in children living with lower exposure. The level of 1-OHPyr in urine is influenced by many factors, including biological variability between subjects (e.g., age, gender, race, health status, nutritional status), cultural differences (e.g., environment, diet, smoking, alcohol, occupation), and variation in the laboratory techniques applied (e.g., sampling design, protocols, analytical precision of the measurement) [21]. Subgroup analysis was conducted to explore the potential confounding factors in this meta-analysis. We found that compared with children living in lower PAHs exposure area, children living with higher PAHs exposure had a higher level of 1-OHPyr in subgroup of developing countries and both genders. The results consist with a cross-sectional study [71] conducted in general population from seven Asian countries. Several studies [72–74] have shown that the concentration of 1-OHPyr was influence by smoking. In this study, we found that the level of 1-OHPyr also higher in children who was exposed to the ETS. The reason was most because of inducing effect of cigarette smoke on CPYs [75]. As for the gender, the pooled estimates showed that the level of 1-OHPyr has statistical differences between boys and girls with heterogeneity of 96%, which may not necessarily mean that the level of 1-OHPyr in girls was higher than that in boys. The inconsistency may be related to the study of Kang et al. [28]; children included in this study have sample bias. First, the study chose four schools which had different PAHs exposure levels in air. Second, the study only enrolled boys in a lower exposure school and enrolled girls in a higher exposure school. Thus, the level of 1-OHPyr in girls in this study was higher than boys. After removing Kang et al. [28] in meta-analysis, the pooled data altered, and the heterogeneity was reduced to 0%. Therefore, we suggest that the levels of 1-OHPyr were not statistically different between boys and girls.

We found that the concentration of 2-OHNap detected in children living with higher environmental PAH exposure was higher than that in the lower exposure area. Li et al. [52] reported that concentration of 2-OHNap was well correlated with total PAH exposure, which indicated the higher level of PAHs in air, and the higher level in urine. There were no statistical differences in the levels of
2-OHNap between boys and girls. However, only two studies were included in the analysis, which may not reflect the real differences. Therefore, studies on 2-OHNap still need to be done to identify the potential differences between genders.

The meta-analysis only compared the concentration of other PAHs metabolites in children living with different environmental exposure. The pooled data showed that the levels of 3-OHPhe and 4-OHPhe detected in children living with lower environmental exposure were higher than those in the higher exposure area. Scinicariello et al. [79] noted that the main source of exposure of the larger PAHs (such as phenanthrene) is dietary, which could lead to the higher concentration of hydroxyphenanthrene found in lower exposure environment.

We conducted a comprehensive search to cover all the available studies measuring PAHs metabolites in children with non-occupational exposure to estimate the level of the PAHs internal exposure and to compare the levels of PAHs internal exposure in various children groups, the findings of which may provide a reference for studies in this area. However, several limitations still need to be considered when interpreting and generalizing the present results. First, some data had been recalculated before putting in the analysis which may influence the accuracy of the pooled estimates. The concentration of 2-OHNap, 1-OHNap, 2-OHFlu, 3-OHFlu, 9-OHFlu, 1-OHPhe, 2-OHPhe, 3-OHPhe, and 4-OHPhe in children aged under 6 years were not pooled due to the lack of data. Second, the level of PAHs in children may be abnormal distribution, and a mean value measures the central tendency, which could also lead to a bias in the estimating of total PAHs metabolites level and meta-analysis. Third, subgroup analyses were conducted by countries, gender, age, type of data, study period, and sample collection season in this study but the heterogeneity were not decrease obviously. In addition, heterogeneity that comes from ethnicity diversity, food intake differences, sample size differences, and health status could not be analyzed in the current meta-analysis, which also needs to be considered when interpreting the pooled results. Besides, we found that combustion of industrial sources and automobile exhaust were the main exposure sources of higher environmental exposure group in this study. However, the subgroup analysis grouping by kind of exposure sources were not conducted due to only one study [44] has tested the 1-OHPyr of children living near to main roads. Fourth, meta-analysis on differences of 1-OHPyr concentration in children and adolescents by age were conducted in children aged 6 to 11 years and 12 to 19 years. The cut-off point of 11 years may not represent a sharp limit, and the difference of levels of 1-OHPyr in children under 6 years group were not analyzed. Further, although majority of children of our included studies were recruited from schools, a small proportion of adolescents (12.11%) aged 12 to 20 years were sampled based on population registry, which may lead to including young people as “non-occupationally exposed” with the same likelihood of school children. Finally, except for 1-OHPyr, there were few studies with small

### Table 5: Urinary concentration of four PAH metabolites between living with higher environmental exposure group and living with lower environmental exposure group

| Metabolites         | No. of studies | Model  | SMD (95% CI) | p    | Heterogeneity |
|---------------------|----------------|--------|--------------|------|--------------|
|                     |                |        |              |      | χ²    | p    | I²  |
| 1-OHNap (Additional file 1: Figure S7) | 2              | Fixed effects | 0.35 [−1.28, 1.99] | 0.67 | 1.59 | 0.21 | 37% |
| 2-OHPhe (Additional file 1: Figure S8)  | 2              | Random effects | 0.02 [−0.11, 0.16] | 0.75 | 5.30 | 0.02 | 81% |
| 3-OHPhe (Additional file 1: Figure S9)  | 3              | Random effects | −0.16 [−0.55, 0.23] | 0.42 | 6.46 | 0.04 | 69% |
| 4-OHPhe (Additional file 1: Figure S11) | 3              | Fixed effects | −0.34 [−0.57, −0.12] | 0.003 | 0.29 | 0.59 | 0%  |

*Sensitivity analysis of meta-analysis on differences of levels of 3-OHPhe in children and adolescents with different living conditions (Additional file 1: Figure S10)*
sample size reported on other ten PAHs metabolites, thus the internal exposure levels in various children groups cannot be accurately analyzed.

Conclusion
In summary, 1-OHPyr is the most widely used biomarker of PAHs. The pooled value of 1-OHPyr in children in this study was higher than the reported reference value of non-occupational people who do not smoke. The present meta-analysis suggests that the level of 1-OHPyr in children and adolescent were in relative high status, especially among the children at younger age. The internal diversity of PAHs exists in children and adolescents. Children and adolescents living with higher environmental exposure and exposed to ETS have higher concentration of 1-OHPyr. There were few studies reported on other PAHs metabolites such as 2-OHNap, 2-OHFlu, 3-OHPhe, and 4-OHPhe, thus more attention needs to be paid on those metabolites in future studies.

Additional file

Additional file 1 Figure S1. Subgroup analysis by countries on differences of levels of 1-OHPyr in children and adolescents with different living conditions. Figure S2. Subgroup analysis by age groups on differences of levels of 1-OHPyr in children and adolescents with different living conditions. Figure S3. Subgroup analysis by gender on differences of levels of 1-OHPyr in children and adolescents with different living conditions. Figure S4. Subgroup analysis by type of data on differences of levels of 1-OHPyr in children and adolescents with different living conditions. Figure S5. Subgroup analysis by study period on differences of levels of 1-OHPyr in children and adolescents with different living conditions. Figure S6. Subgroup analysis by sample collection season on differences of levels of 1-OHPyr in children and adolescents with different living conditions. Figure S7. Meta-analysis on differences of levels of 1-OHPyr in children and adolescents with different living conditions. Figure S8. Meta-analysis on differences of levels of 2-OHPhe in children and adolescents with different living conditions. Figure S9. Meta-analysis on differences of levels of 3-OHPhe in children and adolescents with different living conditions. Figure S10. Sensitivity analysis of meta-analysis on differences of levels of 3-OHPhe in children and adolescents with different living conditions. Figure S11. Meta-analysis on differences of levels of 4-OHPhe in children and adolescents with different living conditions. (DOCX 194 kb)

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Authors’ contributions
QL, XH, and XD conceived and designed the study. XH, XD, WL, SL, and BY designed the selection criteria. XH, XD, and QL screened literature and extracted data. XH, XD, YC, WL, SL, BY, and QL performed the statistical analysis. XH and QL drafted and revised the manuscript. All authors read and approved the final manuscript.

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