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PAH exposure is associated with enhanced risk for pediatric dyslipidemia through serum SOD reduction

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ABSTRACT

Background: Exposure to polycyclic aromatic hydrocarbons (PAHs) is linked to abnormal lipid metabolism, but evidence regarding PAHs as risk factors for dyslipidemia is lacking.
Objective: To investigate the respective role and interaction of PAH exposure and antioxidant consumption in the risk for pediatric dyslipidemia.
Methods: We measured the concentrations of serum lipids, superoxide dismutase (SOD) and urinary hydroxylated PAHs (OH-PAHs) in 403 children, of which 203 were from an e-waste-exposed area (Guiyu) and 200 were from a reference area (Haojiang). Biological interactions were calculated by additive models.
Results: Guiyu children had higher serum triglyceride concentration and dyslipidemia incidence, and lower serum concentration of high-density lipoprotein (HDL) than Haojiang children. Elevated OH-PAH concentration, and concomitant SOD reduction, were both associated with lower HDL concentration and higher hypo-HDL risk ($\sum_3$OH-Phes: B for lgHDL = −0.048, $P < 0.01$; OR for hypo-HDL = 3.708, 95% CI: 1.200, 11.453; SOD: B_{T3} for lgHDL = 0.061, $P < 0.01$; OR_{T3} for hypo-HDL = 0.168, 95% CI: 0.030, 0.941; all were adjusted for confounders). Biological interaction between phenanthrol exposure and SOD reduction was linked to dyslipidemia risk (RERI = 2.783, AP = 0.498, S = 2.537). Children with both risk factors (higher $\sum_3$OH-Phes and lower SOD) had 5.594-times (95% CI: 1.119, 27.958) the dyslipidemia risk than children with neither risk factors (lower $\sum_3$OH-Phes and higher SOD).
Conclusion: High PAH exposure combined with SOD reduction is recommended for predicting elevated risk for pediatric dyslipidemia. Risk assessment of PAH-related dyslipidemia should take antioxidant concentration into consideration.

1. Introduction

Polycyclic aromatic hydrocarbons (PAHs) are a series of organic chemicals with two or more aromatic rings (Kim et al., 2013). They are widespread in daily life, being bound in PM2.5 and as compositions of cigarette smoke, cooking fumes, and vehicle exhaust (Choi et al., 2010; Chou et al., 2017). Furthermore, PAHs are widespread in industrial activities requiring burning of organic fuels, including informal e-waste recycling (Choi et al., 2010; Chou et al., 2017; Guo et al., 2012). Among the multiple sources of PAH exposure, e-waste pollution has aroused much attention (Guo et al., 2012; Zeng et al., 2020, this issue). Guiyu, a town in southeastern China, is one of the largest e-waste recycling and dismantling communities in the world, dismantling 1.7 million tons of e-waste annually (Heacock et al., 2018). Local air, soil, and riverine sediment have been contaminated with PAHs and other pollutants released by e-waste dismantling (Xu et al., 2016; Yekeen et al., 2016; Yu et al., 2006; Zeng et al., 2020, this issue; Zhang et al., 2014). Elevated exposure to multiple e-waste pollutants, including PAHs, heavy metals, polybrominated diphenyl ethers, polychlorinated biphenyls, dioxin-like compounds, bisphenol A, and perfluorooctanoic acid, has been reported

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in Guiyu population (Guo et al., 2012; Liu et al., 2016, 2019; Wu et al., 2010, 2012; Xu et al., 2016; Zeng et al., 2016). Although informal e-waste recycling workshops were moved to a regularized industrial park after 2015, the PAH exposure level in Guiyu is still higher than reference populations (Heacock et al., 2018; Zeng et al., 2020, this issue). Exposed individuals absorb PAHs through the respiratory system, digestive system and skin (Kim et al., 2013; Lao et al., 2018). During phase I metabolism of PAHs in the human liver, superoxide anion ($O_2^{-\bullet}$) and hydrogen peroxide (H_2O_2) are released, contributing to DNA damage and other related outcomes (Jarabak et al., 1998; Wang et al., 2019a). Although PAHs are metabolized and excreted rapidly from the human body (excretion half-life: 2.5–6.1 h), the already produced depurinated DNA adducts, stable DNA adducts, point mutations, and nucleobase oxidation during PAH phase I metabolism are irreversible (Li et al., 2012; Wang et al., 2019a). Oxidative stress mediates PAH-related health outcomes, including abnormal blood pressure, asthma, and impairment of the hematopoietic system (Wang et al., 2017, 2020, 2019b).

Dyslipidemia in childhood and adolescence is a genetic or multifactorial disorder of lipoprotein metabolism (Lozano et al., 2016). Dyslipidemia is not a disease, but rather is a risk factor for cardiovascular disease in adulthood (Lozano et al., 2016). Screening for dyslipidemia in childhood and early dyslipidemia intervention could prevent cardiovascular events in adulthood (Goldstein and Brown, 2015; Grundy et al., 2019; Lozano et al., 2016). High concentrations of triglycerides (TG), total cholesterol (TC) and low-density lipoprotein (LDL) have been regarded as cardiovascular risk factors for three decades (Nordestgaard and Varbo, 2014). TG (2–10 mmol/L, in the form of triglyceride-rich lipoproteins), cholesterol, and LDL (a cholesterol-carrying lipoprotein) enter into the artery wall through a dysfunctional endothelium, contributing to atherosclerosis (Goldstein and Brown, 2015; Nordestgaard and Varbo, 2014). High density lipoprotein (HDL) is a cardioprotective lipoprotein transporting cholesterol from the periphery to the liver for catabolism, and a decrease in HDL is a marker of cardiovascular risk (Rothblat and Phillips, 2010). The definition of dyslipidemia in childhood and adolescence is inconsistent in different countries and populations, making it more difficult for screening and intervention (Force et al., 2016; National Center for Cardiovascular Diseases, China, 2017). In the United States National Health and Nutrition Examination Surveys (Kit et al., 2012, 2015), the prevalence of elevated TC levels ($\geq$200 mg/dL) in Americans 8–17 years of age is 7.8%, and the prevalence of elevated LDL levels ($\geq$130 mg/dL) in US adolescents is 7.4%. In European normal-weight subjects ($\leq$17 years of age) (Martin et al., 2015), the prevalence of high TC (>5.18 mmol/L), LDL (>3.40 mmol/L), TG (>1.71 mmol/L), and low HDL (<0.90 mmol/L) for German/Austrian/Swiss nationals is 9%, 7%, 16%, and 3%. In the same batch (Martin et al., 2015), data for Turkish nationals is 7%, 7%, 10%, and 4%, and for Southern European nationals is 7%, 7%, 10%, and 5%, respectively. A meta-analysis incorporating multiple diagnostic criteria shows that the overall pooled-prevalence of total dyslipidemia in Chinese children and adolescents is 25.3%, and the prevalence of high TC, LDL, TG, low HDL and hyperlipemia in Chinese children and adolescents is 4.1%, 5.3%, 8.5%, 6.8%, and 4.8%, respectively (Ding et al., 2015).

Dyslipidemia is a complex phenotype to which various environmental factors and currently unidentified genetic factors contribute (Force et al., 2016). Positive links between PAH exposure and dyslipidemias have been found in Chinese and Swedish adults by epidemiologic studies (Alhamdow et al., 2017; Ma et al., 2019), but the links in children remain unclear. In depth, several animal experiments have demonstrated the association between PAH exposure and abnormal lipid metabolism, but the results remain inconsistent: both elevated catabolism and elevated anabolism of lipids can be found in the liver (Jin et al., 2014; Loughery et al., 2018; Tanos et al., 2012). As a result, it is still unclear how PAHs affect blood lipid, especially in children, the most vulnerable population.

Oxidative stress, which can be exerted by PAH exposure, has uncertain roles in dyslipidemia. Although oxidative stress can oxidatively modify lipoproteins and LDL, which contributes to foam cell formation and further atherosclerosis (Kattoor et al., 2017; Senoner and Dichtl, 2019), there is no adequate research to identify the association between oxidative stress and blood lipid levels. An epidemiologic study of 100 healthy young adults in Turkey indicated that oxidative stress is positively correlated with serum cholesterol, triglyceride and low-density lipoprotein levels without inquiring about the causal link (Turkdogan et al., 2014). Based on the well-known role of oxidative stress in atherosclerosis, there has long been an interest in the application of antioxidants to prevent atherosclerosis (Senoner and Dichtl, 2019). The induction of superoxide dismutase (SOD), the only enzyme to be able to specifically scavenge $O_2^{-\bullet}$, is a much more effective approach to scavenge oxidant production than exogenous antioxidant supplementation in clinical trials (Lei et al., 2016; Nelson et al., 2006). SOD is critical in protecting the vasculature against oxidative stress (Khosravi et al., 2019). Reduced SOD is associated with atherosclerosis (Khosravi et al., 2019). As a result, serum SOD concentration is used as the biomarker of vascular antioxidant capacity and a target for dyslipidemia prevention in the present study.

The interaction between PAH exposure and SOD reduction in pediatric dyslipidemia has been scarcely studied so far. A biological interaction, instead of a statistical interaction, will be explored in the present study. A biological interaction is where two risk factors are involved in the same pathogenesis of disease (Ahlbom and Alfredsson, 2005), and can be assessed based on the statistical interaction in the additive model (Ahlbom and Alfredsson, 2005; Andersson et al., 2005). On the contrary, most analyses of statistical interaction implicitly utilize the multiplicative scale (Ahlbom and Alfredsson, 2005).

Although previous studies indicate that e-waste exposure does harm to the blood lipid and cardiovascular system, more epidemiological investigations in children, a vulnerable population, are needed to confirm the association between multiple pollutants and blood lipid (Grant et al., 2013; Lu et al., 2018). We previously reported an association between child blood lipids and e-waste lead exposure (Lu et al., 2018), but the association between child blood lipids and e-waste PAH exposure remains unclear. The main goal of this study is to investigate the role of PAH exposure, concomitant SOD decrease, and their biological interaction in pediatric dyslipidemia. We hypothesized that PAH exposure and concomitant SOD reduction contribute to pediatric dyslipidemia, and the biologically additive interaction between PAH exposure and SOD reduction contributes to enhanced risk for pediatric dyslipidemia. We evaluated this hypothesis in a cross-sectional study of children from Guiyu (an e-waste recycling area contaminated by multiple toxic pollutants) and Haojiang (a reference area).

2. Materials and methods

2.1. Study population

Subjects were enrolled from November to December 2016 in the study and comprised 403 healthy children 2–7 years of age, including 203 from Guiyu (exposed group) and 200 from Haojiang (reference group). Guiyu, with a more than 40-year history of informal e-waste recycling, is one of the best-known e-waste-contaminated areas (Dai et al., 2020, this issue; Zeng et al., 2020, this issue). Haojiang, a non-e-waste-contaminated area located 31.6 km to the east of Guiyu, has similar characteristics in lifestyle and cultural background with Guiyu (Wu et al., 2010; Zeng et al., 2020, this issue). The detailed information about both areas has been described in our previous studies (Wu et al., 2010; Zeng et al., 2020, this issue). Every participant's guardians signed an informed consent, and completed a questionnaire including modules about residential setting, living habits, family economic and cultural levels, e-waste-contact circumstances, and family history of chronic diseases. Fasting elbow venous blood was taken using anticoagulative plain tubes for isolating serum, and then stored at −80 °C until assay. Morning urine was collected in BD tubes, and then stored at −20 °C until

assay. All protocols in the present study were approved by the Human Ethics Committee of Shantou University Medical College, China.

2.2. Blood biomarker analysis and definition

Concentrations of blood lipids, including serum TG, TC, LDL, and HDL, were measured by an Automatic Biochemical Analyzer (TBA-40FR, Toshiba Medical System Corporation, Japan). Pediatric dyslipidemia was defined as having at least one of the following outcomes (National Center for Cardiovascular Diseases, China, 2017; Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents, 2011): TC $\geq$ 5.18 mmol/L (hyper-TC), LDL $\geq$ 3.37 mmol/L (hyper-LDL), HDL $<$ 1.04 mmol/L (hypo-HDL), TG $\geq$ 1.13 mmol/L (0–9 years of age) or 1.47 mmol/L (10–19 years of age) (hyper-TG).

Serum SOD concentration was measured with an enzyme-linked immunosorbent assay kit (catalog No. LS-F4233, LifeSpan BioSciences, Inc., America). In the absence of a reference threshold, the risk threshold of SOD used in the present study is the median of SOD in the children whom we measured (SOD $<$ 75.450 ng/mL is defined as low SOD).

2.3. PAH exposure analysis

Eight hydroxylated metabolites of PAHs (OH-PAHs) in urine were measured by gas chromatography-mass spectrometry (Agilent 7890A-5975C) based on Campo's method (Campo et al., 2008), including 1-hydroxynaphthalene (1-OH-Nap), 2-hydroxynaphthalene (2-OH-Nap), 2-hydroxyfluorene (2-OH-Flu), 9-hydroxyfluorene (9-OH-Flu), 2-hydroxyphenanthrene (2-OH-Phe), 4-hydroxyphenanthrene (4-OH-Phe), 9-hydroxyphenanthrene (9-OH-Phe), and 1-hydroxypyrene (1-OH-Pyr). Targeted analytes included urinary monohydroxy metabolites of several 2-, 3-, and 4-ring PAHs listed as the U.S. EPA's sixteen priority PAHs (Keith and Telliard, 1979). Monohydroxy metabolites of PAHs with more than 4 rings in urine were not measured in the present study because they were mainly excreted by feces instead of urine (Chipman et al., 1982, 1981). Reagent brands/models, sample procedures, and quality control were introduced in detail in our previous article (Wang et al., 2020). In brief, 5 mL urine supernatant was incubated with 20 μL β-glucuronidase/sulphatase and 20 μL mixed internal standard (containing 1-OHNap-D7, 20 mg/L in acetonitrile, and 1-OHPyr-D9, 2 mg/L in acetonitrile) overnight at 37 °C, pH5.0. After being restored to room temperature and adding $MgSO_4{\cdot}7H_2O$, the urine samples underwent liquid–liquid extraction three times with n-hexane. After concentrating to dryness under nitrogen, samples were silylated with 100 μL 99% BSTFA + 1%TMCS at 90 °C for 45 min, and then quantitatively determined by GC–MS. Quantitation was carried out by the internal standard method. Standard curves were constructed using concentration gradients of mixed standard solution (0–640 μg/L for 1-OH-Nap and 2-OH-Nap, and 0–64 μg/L for other OH-PAHs). The linearity of the calibration curves was excellent (r^2 ranged from 0.995 to 0.999). Relative standard deviations (RSDs) ranged from 0.71% to 4.74%. Spiked recoveries ranged from 84.56% to 117.38%. The $\sum_8$OH-PAHs was defined as the sum of eight congeners in the urine. $\sum_2$OH-Naps was defined as the sum of 1-OH-Nap and 2-OH-Nap. $\sum_2$OH-Flus was defined as the sum of 2-OH-Flu and 9-OH-Flu. $\sum_3$OH-Phes was defined as the sum of 2-OH-Phe, 4-OH-Phe, and 9-OH-Phe.

2.4. Statistical analysis

Correlations were evaluated by Spearman correlation analysis. Stepwise linear regression (B, 95% CI, and *P*), logistic regression (ORs and 95% CIs) and tertile regression models (tertile 1 as the reference) were used to estimate the associations between PAH exposure, serum SOD and serum lipid levels. Biological interaction between PAH exposure and antioxidants, linked to dyslipidemia, was calculated by the method described previously by Andersson et al. (2005). In brief, three measures are presented for biological interaction: the relative excess risk due to interaction (RERI), the attributable proportion due to interaction (AP), and the synergy index (S) (Andersson et al., 2005). If there is no biological interaction, RERI and AP are equal to 0 and S is equal to 1 (Andersson et al., 2005). Statistical analyses were performed with SPSS version 22.0 (IBM Corporation, NJ, USA). Data were graphed using GraphPad Prism 8.0 (GraphPad, San Diego, CA) and Microsoft Excel (Excel 2016, Microsoft, Redmond, WA, USA; the preset sheet was designed by T. Andersson, L. Alfredsson, H. Källberg, S. Zdravkovic, and A. Ahlbom) (Andersson et al., 2005). Significance was set at $P < 0.05$ (two-tailed). Normally distributed data are expressed as mean ± standard deviation (SD), whereas non-normally distributed data are presented as median (P25, P75). Chi-squared, Mann-Whitney *U*, and independent-sample t tests were used to evaluate the differences between groups. Missing values were deleted in descriptive analyses and regression models.

3. Results

3.1. General characteristics of subjects

Age and gender in Guiyu children and Haojiang children did not differ, but socioeconomic level and physical development indices were lower in Guiyu children than Haojiang children, and urinary OH-PAH concentrations were higher in Guiyu children than Haojiang children, all of which have been described previously (Wang et al., 2020). Family histories of obesity and diabetes did not significantly differ between Guiyu and Haojiang children (Table 1). Compared with Haojiang children, Guiyu children had a greater probability of e-waste exposure, higher $\sum_8$OH-PAHs > median percent, animal-oil intake percent, serum TG concentration, dyslipidemia incidence, hyper-TG incidence, and lower serum HDL concentration (Table 1).

Factors affecting PAH-exposure levels in the present study were screened, by stepwise logistic regression, from potential factors including the place of residence, gender, age, BMI, e-waste contact, residence in the workplace, parent occupation involving e-waste recycling, cooking oil use, negative smoking, parental education level, and average household monthly income. The results showed that, in total children, living in Guiyu (OR = 1.888, 95% CI: 1.138, 3.131) and BMI (OR = 1.164, 95% CI: 1.007, 1.347) were risk factors for higher PAH exposure (urinary $\sum_8$OH-PAHs > 5.92 μg/L, the median). In Guiyu children, the risk factor for higher PAH exposure was residence as an e-waste workplace (OR = 2.089, 95% CI: 1.077, 4.053), while a protective factor was use of an extremely small amount of cooking oil (OR = 0.064, 95% CI: 0.006, 0.705). In Haojiang children, risk factors for higher PAH exposure were e-waste contact (occasionally being brought to an e-waste recycling area) (OR = 3.778, 95% CI: 1.488, 9.593) and cooking with vegetable-oil dominant cooking oils (OR = 2.070, 95% CI: 1.041, 4.118).

3.2. Association of PAHs with dyslipidemia

Our results indicate a positive role for PAH exposure in dyslipidemia. Compared with children exposed to lower phenanthrene ($\sum_3$OH-Phes < median), children exposed to higher phenanthrene had lower HDL concentrations (Fig. 1). HDL was negatively correlated with $\sum_3$OH-Phes ($r = -0.111$, $P < 0.05$), and an increase in $\sum_3$OH-Phes concentration was associated with a decrease in lgHDL before and after adjusting for potential confounders (Table 2). Either before or after adjusting for potential confounders, elevated levels of $\sum_3$OH-Phes were significantly associated with increased hypo-HDL risk (Table 2). In summary, phenanthrene exposure is a risk factor for hypo-HDL. No significant association was found between PAH and other lipid indicators including TC concentration, LDL concentration, TG concentration, hyper-TC risk, hyper-LDL risk, and hyper-TG risk (all $P > 0.05$).

Table 1
Demographic characteristics of the study population.

Characteristics	Guiyu		Haojiang		*P*-value
	n	Median (P25, P75) or n (rate) or Mean ± SD	n	Median (P25, P75) or n (rate) or Mean ± SD	
Family history of obesity [n (%)]	200	4 (2.0%)	200	4 (2.0%)	1.000[a]
Family history of diabetes [n (%)]	200	28 (14.0%)	200	16 (8.0%)	0.055[a]
E-waste contact	202		200		<0.001[a]
None		116 (57.4%)		173 (86.5%)	
Occasionally		73 (36.1%)		27 (13.5%)	
Almost everyday		13 (6.4%)		0 (0.0%)	
Residence in the workplace	192	87 (45.3%)	200	14 (7.0%)	<0.001[a]
Father in e-waste recycling occupation	196	44 (22.4%)	199	2 (1.0%)	<0.001[a]
Mather in e-waste recycling occupation	192	7 (3.6%)	199	0 (0.0%)	0.007[a]
Cooking oil	199		200		<0.001[a]
Predominantly animal oil		24 (12.1%)		2 (1.0%)	
Predominantly vegetable oil		66 (33.2%)		136 (68.0%)	
Both		101 (50.8%)		61 (30.5%)	
Seldom use either		8 (4.0%)		1 (0.5%)	
Urine $\sum_8$OH-PAHs > 5.92 μg/L (the median) [n (%)]	201	113 (56.2%)	200	87 (43.5%)	0.011[a]
LDL (mmol/L)	191	2.24 (1.92, 2.51)	194	2.28 (1.89, 2.59)	0.663[b]
TG (mmol/L)	191	0.74 (0.58, 0.94)	194	0.61 (0.51, 0.74)	<0.001[b]
TC (mmol/L)	191	3.98 ± 0.61	194	4.06 ± 0.57	0.173[c]
HDL (mmol/L)	191	1.35 (1.18, 1.49)	194	1.46 (1.30, 1.70)	<0.001[b]
Dyslipidemia [n (%)]	191	45 (23.6%)	194	19 (9.8%)	<0.001[a]
TC ≥ 5.18 mmol/L [n (%)]	191	9 (4.7%)	194	4 (2.1%)	0.150[a]
LDL ≥ 3.37 mmol/L [n (%)]	191	7 (3.7%)	194	3 (1.5%)	0.324[a]
HDL < 1.04 mmol/L [n (%)]	191	19 (9.9%)	194	11 (5.7%)	0.117[a]
TG ≥ 1.13 mmol/L [n (%)]	191	24 (12.6%)	194	7 (3.6%)	0.001[a]

Dyslipidemia is defined as the presence of any one of the following four factors: TC ≥ 5.18 mmol/L, LDL ≥ 3.37 mmol/L, HDL < 1.04 mmol/L, TG ≥ 1.13 mmol/L.

[a] Chi-square test.
[b] Independent- sample nonparametric test.
[c] Independent samples *t*-test.

3.3. Association of PAHs with serum SOD concentration

Serum SOD concentrations in different groups and the association between higher $\sum_8$OH-PAHs and lower SOD have been described in our previous study (Wang et al., 2020). In the present study, associations between SOD and different OH-PAH subgroups were explored. Serum SOD concentration was negatively correlated with $\sum_2$OH-Flus (r = −0.193, P = 0.018) but not $\sum_2$OH-Naps (r = −0.156, P = 0.058), $\sum_3$OH-Phes (r = 0.019, P = 0.816), or 1-OH-Pyr (r = −0.092, P = 0.263). Linear regressions showed that higher $\sum_2$OH-Naps, $\sum_2$OH-Flus and $\sum_3$OH-Phes were all associated with lower lgSOD, but not 1-OH-Pyr [$B_{\sum 2OH\text{-}Naps\text{-}T3}$ = −0.062, 95%CI (−0.116, −0.009), P = 0.023, in Guiyu children but not in Haojiang children; $B_{\sum 2OH\text{-}Flus}$ = −0.122, 95%CI (-0.215, −0.029), P = 0.011, in total children; $B_{\sum 3OH\text{-}Phes}$ = −0.103, 95%CI (−0.188, −0.018), P = 0.018, in total children; and $B_{1\text{-}OH\text{-}Pyr}$ = −0.030, 95%CI (−0.179, 0.119), P = 0.690, in total children. All were adjusted for residence, gender, age, BMI, cooking oil, passive smoking, level of parent education and family income]. Furthermore, dose effects on serum SOD were found in naphthalene exposure and fluorene exposure (Fig. 2). Between-group comparisons [OH-PAH-T1 vs. OH-PAH-T2 vs. OH-PAH-T3] showed that serum SOD concentration was significantly reduced with increasing $\sum_3$OH-Naps (non-parametric test P between three groups < 0.05) and $\sum_2$OH-Flus (Ps for the non-parametric test between three groups and the post hoc test between T2 and T3 groups were both < 0.05); The associations of SOD with $\sum_2$OH-Naps and $\sum_2$OH-Flus were both stronger at high doses (T3, P for B < 0.05) than at middle doses (T2, P for B > 0.05). In summary, higher PAH exposure was linked to lower serum SOD concentration.

3.4. Association of serum SOD concentration with dyslipidemia

Children with lower SOD (serum SOD concentration < 75.450 ng/mL, the median) had lower HDL concentrations than children with higher SOD (serum SOD concentration > 75.450 ng/mL) (Fig. 1). HDL was positively correlated with SOD (r = 0.286, P < 0.001). An increase in serum SOD concentration was associated with an increase in serum HDL concentration before and after adjusting for potential confounders (Table 2). After adjusting for potential confounders, the OR for hypo-HDL in the highest SOD tertile was only 16.8% of the OR for hypo-HDL in the lowest tertile of SOD (Table 2). In summary, a high level of serum SOD (serum SOD in the highest tertile) was a protective factor for pediatric hypo-HDL, suggesting a dose-responsive beneficial effect of SOD on blood lipid.

3.5. Biological interaction between PAH exposure and SOD play roles in dyslipidemia

There was a biological interaction (assessed in an additive statistical model) for dyslipidemia risk between high phenanthrene exposure (factor 1, $\sum_3$OH-Phes > 0.998 μg/L) and low serum SOD (factor 2, serum SOD < 75.450 ng/mL). The effect of having both factors on dyslipidemia risk was larger than the sum of the individual effects of factor 1 and factor 2 on dyslipidemia risk (Table 3 and Fig. 3). After adjusting for confounding factors, the combination of higher $\sum_3$OH-Phes (>0.998 μg/L, the median) and lower SOD (<75.450 ng/mL, the median) conferred 5.594-times the dyslipidemia risk compared with children who had both lower $\sum_3$OH-Phes (<0.998 μg/L) and higher SOD (>75.450 ng/mL). On the other hand, interactions between SOD and $\sum_2$OH-Naps, $\sum_2$OH-Flus, or 1-OH-Pyr did not contribute to significant risk for dyslipidemia.

4. Discussion

4.1. PAH exposure and pediatric dyslipidemia

Urinary hydroxylated metabolites of PAHs can be used as biomarkers of short-term PAH exposure (Li et al., 2012; Oliveira et al., 2017). In the current study, the major source of PAH exposure in Guiyu was e-waste recycling. This is consistent with previous studies in Guiyu and other e-waste recycling areas including Taizhou, Qingyuan, Agbogbloshie, New Delhi, Kolkata, Mumbai, and Chennai (Asamoah et al., 2019; Chakraborty et al., 2019; Chen et al., 2016; Feldt et al., 2014; Gu et al., 2010; Huo et al., 2019; Zeng et al., 2020, this issue; Zheng et al., 2019). The open burning of e-waste has released large amounts of PAHs, leading to PAH-contaminated soil, sediment, air and human biospecimens (Heacock et al., 2016; Wang et al., 2012; Xu et al., 2016; Yu et al., 2006; Zeng et al., 2020, this issue; Zhang et al., 2011). Compared with the reference area, according to our previous research, higher PAHs or OH-PAHs can be detected in peripheral venous blood, umbilical cord blood and urine of puerperae, newborns, and children in Guiyu, linked to informal e-waste recycling activities (Cheng et al., 2020, this issue; Guo et al., 2012; Huang et al., 2020; Huo et al., 2019; Xu et al., 2015, 2013; Zheng et al., 2019). In the current study, among the eight OH-PAHs analyzed, $\sum_2$OH-

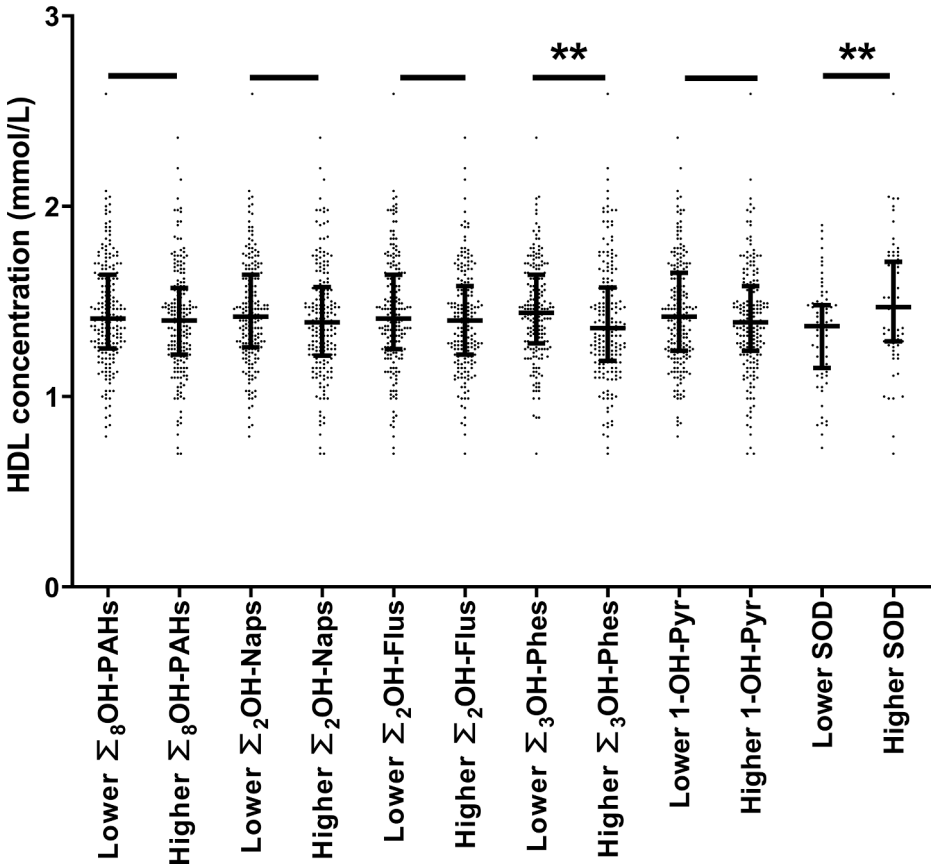

Fig. 1. Comparison of HDL concentrations in child serum. Abscissas: groups. Line at the median and interquartile range. "Lower" and "Higher" are defined by the medians. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, analyzed by the Mann-Whitney test.

Table 2
Factors for HDL concentration and hypo-HDL risk in all participants.

Factors	$\sum_3$OH-Phes	SOD		
Stratify	Total	T1	T2	T3
B (95% CI) for lgHDL [a]	−0.047 (−0.080, −0.014) **	0	0.031 (−0.006, 0.068)	0.066 (0.029, 0.103) **
B (95% CI) for lgHDL [b]	−0.048 (−0.081, −0.015) **	0	0.029 (−0.008, 0.066)	0.061 (0.024, 0.098) **
OR (95% CI) for hypo-HDL [c]	3.206 (1.103, 9.323)	NA	NA	NA
OR (95% CI) for hypo-HDL[d]	3.708 (1.200, 11.453)	1	0.370 (0.084, 1.634)	0.168 (0.030, 0.941)

[a,b]Results of linear regressions. [c,d] Results of logistic regressions. [a, c] Unadjusted model. [b, d] Adjusted for residence, gender, age, BMI, cooking oil, passive smoking, parent education degree, family income, family history of obesity, and family history of diabetes. ** $P < 0.01$. T1: the lowest tertile, T2: the middle tertile, T3: the highest tertile. In tertile regression, T1 is the reference. NA: the model cannot be established.

Naps is the dominant compounds, which is consistent with a study detecting twelve OH-PAHs in 306 urine samples collected from seven Asian countries (China, India, Japan, Korea, Kuwait, Malaysia, and Vietnam) (Guo et al., 2013).

In the present study, higher TG concentrations, higher hyper-TG rates, higher dyslipidemia rates, and lower HDL concentrations are found in e-waste-exposed children. This is consistent with our previous study in the same e-waste recycling area (Lu et al., 2018). In view of the population in the present study, childhood dyslipidemia is defined by the criteria in the Report on Cardiovascular Diseases in China 2017 (National Center for Cardiovascular Diseases, China, 2017), and the reference for the criteria (Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents, 2011). Choosing an appropriate criterion considering racial differences could exclude the possible influence of racial differences on our results.

The present study indicates that an increase in phenanthrene exposure can predict an HDL decrease and a hypo-HDL risk in children. To our knowledge, the present study is the first to analyze dyslipidemia risk related to PAH exposure in children. Data in adults cannot be extrapolated to children, so the present study provides an important reference for dyslipidemia risk assessment of PAH exposure in children. The same trend was observed in a previous epidemiologic study on a U.S. household population (over 18 years old), where naphthalene exposure was associated with decreased HDL possibly through endocrine disruption, lipolysis inhibition, oxidative stress and inflammation (Hu et al., 2015). Epidemiologic studies investigating the effect of PAHs on blood lipids are very limited, where significant and weak associations between PAH exposure and blood lipids have both been found in adults (Alhamdow et al., 2017; Ma et al., 2019). The controversial associations in different studies may be explained by different population characteristics and sample sizes (Alhamdow et al., 2017; Ma et al., 2019). Underlying mechanisms of the associations suggested by previous studies are activation of aryl hydrocarbon receptor signaling pathway, hormone suppression, disordered hepatic lipid metabolism, and disordered lipid-transport links between liver and blood (Jin et al., 2014; Li et al., 2019; Loughery et al., 2018; Ma et al., 2019; Ortiz et al., 2014; Wang et al., 2015). Oxidative stress has not received much attention within the field.

4.2. PAH exposure and SOD consumption

Measurement of SOD, an important member of the antioxidant system and the only enzyme able to specifically scavenge $O_2^{-\bullet}$, can provide a

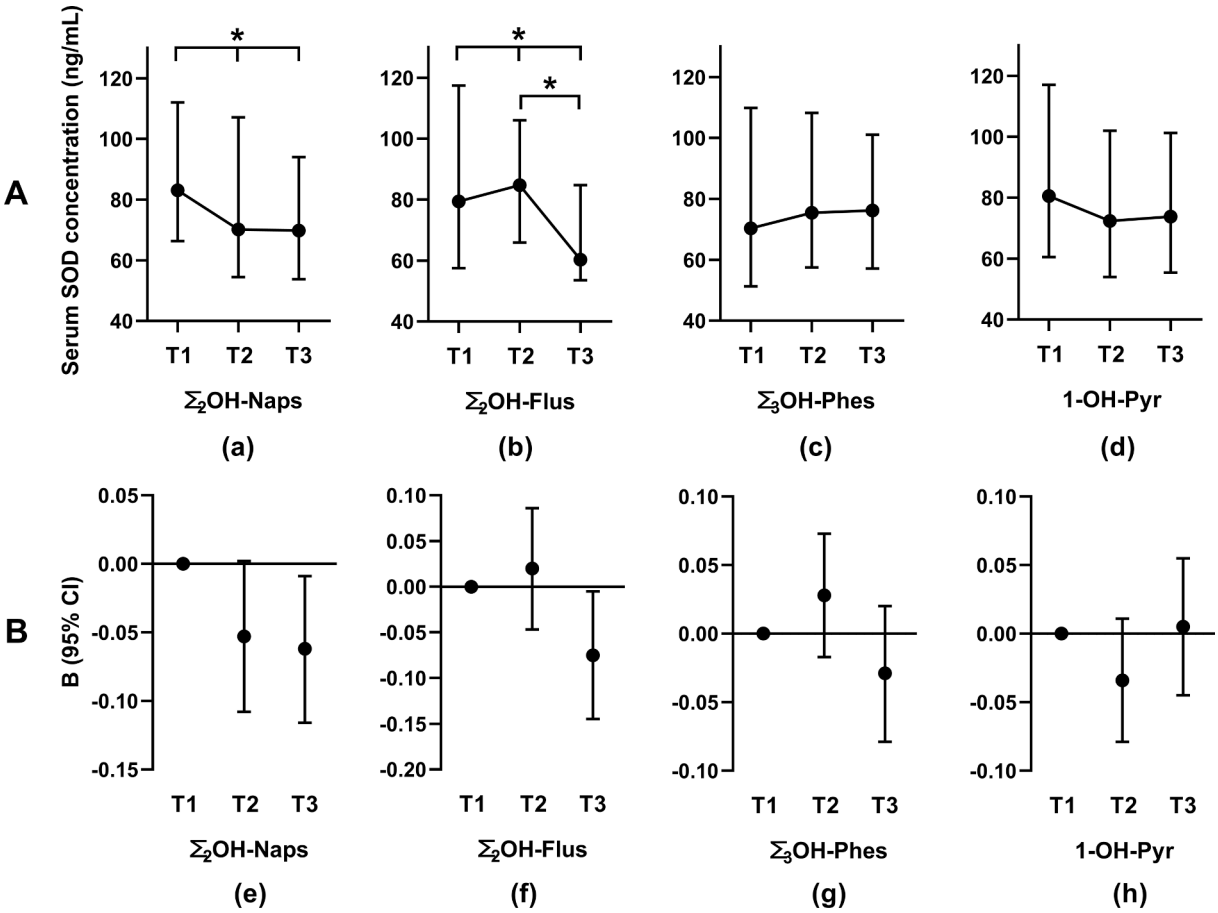

Fig. 2. Dose-response effects of exposures to different PAH subgroups on serum SOD concentration. A. Comparisons of SOD concentrations between three groups [low dose group (children in the lowest tertile of PAH exposure, T1) vs. middle dose group (children in the middle tertile of PAH exposure, T2) vs. high dose group (children in the highest tertile of PAH exposure, T3)]. Line at the median and interquartile range of serum SOD concentration. * $P < 0.05$, analyzed by the Kruskal-Wallis test. (a) $\sum_2$OH-Naps-T1 group vs. $\sum_2$OH-Naps-T2 group vs. $\sum_2$OH-Naps-T3 group. (b) $\sum_2$OH-Flus-T1 group vs. $\sum_2$OH-Flus-T2 group vs. $\sum_2$OH-Flus-T3 group. (c) $\sum_3$OH-Phes-T1 group vs. $\sum_3$OH-Phes-T2 group vs. $\sum_3$OH-Phes-T3 group. (d) 1-OH-Pyr-T1 group vs. 1-OH-Pyr-T2 group vs. 1-OH-Pyr-T3 group. B. Tertile linear regressions between OH-PAHs and lgSOD, with OH-PAH-T1 as the reference. (e) Adjusted model in Guiyu children. Adjusted models in total children and Haojiang children are not listed because of nonsignificant associations. Unadjusted models cannot be built. (f) Unadjusted model in total children. Adjusted models are not listed because of nonsignificant associations. (g)(h) Adjusted models in total children. Unadjusted models could not be built. Adjusted models were all adjusted for residence, gender, age, BMI, cooking oil, passive smoking, parent education levels, and family income.

quantitative biomarker indicating $O_2^{-\bullet}$-scavenging capacity and oxidative stress caused by $O_2^{-\bullet}$ (Sheng et al., 2014). In the current study, exposure to naphthalene, fluorene and phenanthrene were all associated with lower SOD, and the associations of SOD with naphthalene and fluorene were dose-dependent. The discovery indicates an increased $O_2^{-\bullet}$ oxidative stress and antioxidant consumption related to different levels of PAH exposure. Consistently, our previous study in the same sites showed that malonaldehyde concentration (a biomarker for lipid peroxidation) and total SOD activity (U/ml) in serum from Guiyu children were significantly higher than in reference children, indicating an increased oxidative stress and an adaptively increased antioxidant capacity in e-waste-exposed children (Zheng et al., 2013). In another e-waste recycling area located in Longtang, China, PAH exposure contributed from e-waste recycling activities has been associated with higher 8-hydroxy-2′-deoxyguanosine and malondialdehyde (two biomarkers of oxidative stress) in people living near e-waste dismantling sites (Lu et al., 2016). Similar associations have been also found in occupationally-exposed population and general population: In coke oven workers in China, urinary OH-PAHs are significant determinants in the dose-related increase of oxidative damage to DNA (8-hydroxydeoxyguanosine) and lipids (8-*iso*-prostaglandin-F2α) (Kuang et al., 2013); In 3- to 12-year-old children in Ghana, the ΣOH-PAHs, 2-OH-Nap, 2–3-OH-Flu, and 2-,1–9-,4-OH-Phe show a positive correlation with malonaldehyde, while 4-OH-Phe shows a positive correlation with 8-OHdG, suggesting lipid peroxidation related to high PAH exposure (Bortey-Sam et al., 2017). Similar results found in animals and in vitro experiments also support our findings (Ke et al., 2018; Santana et al., 2018). A reasonable explanation for the associations between elevated PAHs and reduced SOD in the present study could be that SOD protects cells from ROS produced by PAHs in vivo: PAH o-quinones (phase I metabolites of PAHs) undergo redox cycling catalyzed by two-electron reductases to generate ROS, but the cycling can be interrupted by SOD (Jarabak et al., 1998).

4.3. SOD consumption and pediatric dyslipidemia

The protective role of a high concentration of SOD (in the highest SOD tertile) in hypo-HDL in the present study is consistent with previous studies that focus on the preventive or therapeutic role of antioxidants (Nelson et al., 2006; Senoner and Dichtl, 2019). Oxidative stress has long been studied in animals and humans as a preventive or therapeutic target in dyslipidemia, and further atherosclerosis, because it is involved in various molecular mechanisms that contribute to foam cell formation and vascular damage (Kattoor et al., 2017; Matsuzawa et al., 2007; Pinzon-Diaz et al., 2018; Senoner and Dichtl, 2019). Oxidative modifications of lipoproteins and LDL lead to abnormal LDL uptake, resulting

Table 3
Biological interaction for dyslipidemia between $\sum_3$OH-Phes and SOD.

Factor 1	Factor 2	RR (95% CI) for dyslipidemia	
$\sum_3$OH-Phes > 0.998 μg/L [b]	SOD < 75.450 ng/mL [c]	Unadjusted model	Adjusted model [a]
+	+	4.267 (1.338, 13.611)	5.594 (1.119, 27.958)
–	+	1.358 (0.390, 4.721)	1.570 (0.283, 8.701)
+	–	1.896 (0.555, 6.482)	2.242 (0.390, 12.883)
–	–	1	1
Measures for interaction		Estimates and 95%CIs	
RERI		2.013 (−1.551, 5.577)	2.783 (−4.588, 10.155)
AP		0.472 (−0.134, 1.077)	0.498 (−0.354, 1.349)
S		2.605 (0.315, 21.527)	2.537 (0.201, 32.036)

RERI, the relative excess risk due to interaction. AP, the attributable proportion due to interaction. S, the synergy index.

[a] Adjusted for gender, age, BMI, cooking oil, passive smoking, parent education degree, family income, family history of obesity, and family history of diabetes.

[b] The threshold value, 0.998 μg/L, was the median of $\sum_3$OH-Phes in total children.

[c] The threshold value, 75.450 ng/mL, was the median of serum SOD concentration in total children.

in lipid accumulation and further oxidative stress in arterial walls (Colles et al., 2001; Huang et al., 2014; Hurtubise et al., 2016; Kattoor et al., 2017; Munzel et al., 2017; Navab et al., 2004; Senoner and Dichtl, 2019). The curative effect of SOD induction observed in previous clinical trials confirmed the risk role of oxidative stress and the protective role of SOD in human atherosclerosis (Nelson et al., 2006; Senoner and Dichtl, 2019). Consistently, mouse experiments also found that an SOD mimic is able to improve lipid profile, probably by reducing superoxide anions and ROS formation, restoration of endothelial NOS activity and NO levels, improvement of vasorelaxation, and reduction of pro-inflammatory cytokines (Reis, 2017; Viana Goncalves et al., 2017). These consistent results should encourage scientists to continue antioxidant-related research in the prevention and treatment of dyslipidemia and atherosclerosis (Nelson et al., 2006; Senoner and Dichtl, 2019).

4.4. Biological interactions between PAH exposure and SOD consumption contribute to an excess risk for pediatric dyslipidemia

Biological interaction, assessed by a statistical additive model, implies more biological significance than multiplicative interaction (Ahlbom and Alfredsson, 2005). A biological interaction between two factors reflects a same pathogenesis in which the two risk factors involved (Ahlbom and Alfredsson, 2005; Andersson et al., 2005).

In the present study, dyslipidemia risk due to phenanthrene exposure appears to be more pronounced in subjects with lower SOD concentrations, and dyslipidemia risk due to SOD reduction appears to be more pronounced in subjects exposed to higher levels of phenanthrenes. The biological interaction indicates that the increased risk for dyslipidemia due to the combination of phenanthrene exposure and antioxidant deficiency is more than the risks attributed to either phenanthrene exposure or antioxidant deficiency alone. In other words, the significant interaction suggests that a reduction in antioxidant concentration may confer an excess dyslipidemia risk in children exposed to high levels of phenanthrenes, and antioxidant therapy could be more effective in children exposed to higher levels of phenanthrene.

Although the respective roles of PAH exposure and SOD deficiency in dyslipidemia have been adequately studied, there is no research focusing on the interaction between PAH exposure and SOD reduction, which plays a role in dyslipidemia. Clinical trials have reported that the benefit of antioxidants varies based on the oxidative status of each individual, with people having increased levels of oxidative stress benefitting more than people with low amounts of ROS (Senoner and Dichtl, 2019). On this basis, a reasonable explanation for the interaction we found between phenanthrene and SOD could be as follows: ROS generated during phenanthrene in-vivo metabolism produces more oxidative stress in phenanthrene-exposed children, so PAH-exposed children should benefit more from SOD and are affected more by SOD deficiency than children who already have low amounts of ROS.

4.5. Strengths and limitations

The present study can provide a reference for pediatric-dyslipidemia prevention in Chinese children and e-waste-exposed populations. In the present study, biological interactions assessed in statistical additive models are performed using SPSS (IBM Corporation, NJ, USA) based on the method designed by Andersson et al. (Ahlbom and Alfredsson, 2005; Andersson et al., 2005), which can be generalized to other studies as a simple approach to biological-interaction calculation.

Several limitations of this study still need to be considered. First, the cross-sectional design of the present study does not allow us to demonstrate a causal relationship between PAH exposure and dyslipidemia. Large-sample cohort studies and clinical trials in the future are needed to explore the causal relationship. Second, due to the limited volume of samples, the present study measured only eight urinary PAH metabolites, and does not exclude the influence of other toxic substances on dyslipidemia. However, results in the present study are still meaningful since we have included urinary metabolites of 2-, 3-, 4-ring PAHs, considering that metabolites from PAHs with more than four benzene rings mainly excreted through feces (Chipman et al., 1982, 1981). Future studies should evaluate other PAHs and other pollutants, and focus on the joint influences of various pollutants on dyslipidemia risk. Third, as PAH metabolism and excretion are rapid in the human body, the concentrations of urine OH-PAHs reflect temporary exposure levels, instead of chronic exposure or long-term exposure levels. However, the present study is still meaningful because Guiyu children are exposed to PAHs continuously, and the already produced DNA adducts and oxidative damage are irreversible. Fourth, dyslipidemia is a complex phenotype resulting from environmental contributions and genetic factors, but the present study does not exclude the influence of genetic factors, although we have adjusted for related family histories. Further studies are required to investigate the genetic-environmental interaction in the development of pediatric dyslipidemia.

5. Conclusions

This is the first study to find that the biological interaction between PAH exposure and antioxidant consumption is linked to risk for pediatric dyslipidemia. The present study indicates that PAH exposure and concomitant SOD reduction both contribute to pediatric dyslipidemia risk, and the additive interaction between PAH exposure and SOD reduction contributes to an excess risk for pediatric dyslipidemia compared to the sum of their single risks. These findings provide a deep insight into the synergistic effects of PAH exposure and oxidative stress on pediatric dyslipidemia risk, suggesting that risk assessment of PAH-related dyslipidemia should take antioxidant concentration into consideration. Concentrations of urine OH-PAHs and serum SOD are recommended by this study as biomarkers for predicting pediatric dyslipidemia risk. SOD supplements are recommended by this study as an intervention for PAH cardiovascular toxicity.

CRediT authorship contribution statement

Qihua Wang: Investigation, Formal analysis, Software, Writing - original draft. **Xijin Xu:** Conceptualization, Project administration,

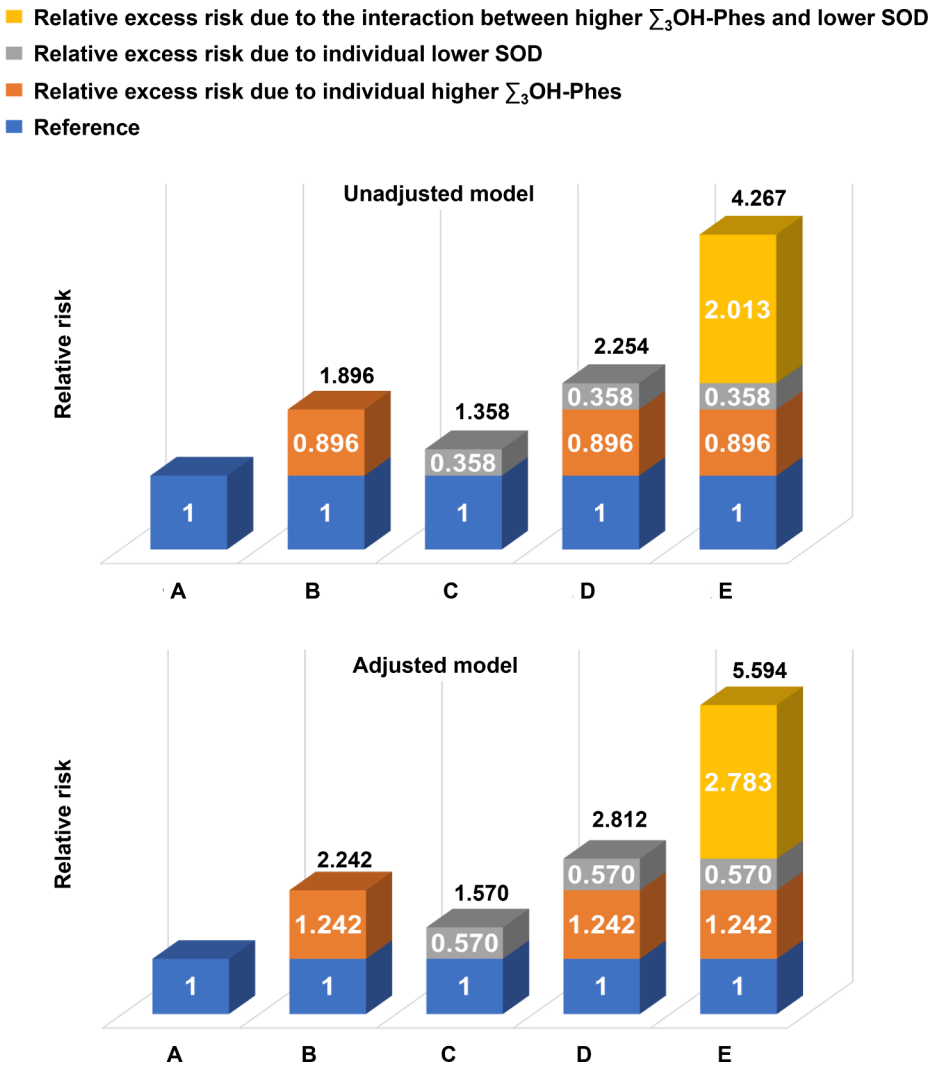

Fig. 3. Relative risk (RR) for pediatric dyslipidemia with contributions from different factors marked. Abscissas: category. Y-axes: RR values estimated from multinomial logistic regressions. Lower SOD is defined as a serum SOD < 75.450 ng/mL (the median). Higher $\sum_3$OH-Phes is defined as a urinary $\sum_3$OH-Phes > 0.998 μg/L (the median). Interactions between higher $\sum_3$OH-Phes (factor 1) and lower SOD (factor 2) are estimated for pediatric-dyslipidemia risk. A. Children with lower $\sum_3$OH-Phes and higher SOD (with neither factor); B. Children with higher $\sum_3$OH-Phes and higher SOD (with only factor 1); C. Children with lower $\sum_3$OH-Phes and lower SOD (with only factor 2); D. The sum of $RR_{only\text{-}factor\text{-}1}$ and $RR_{only\text{-}factor\text{-}2}$; E. Children with higher $\sum_3$OH-Phes and lower SOD (with both factor 1 and factor 2). The concurrent presence of factor 1 and factor 2 contributes a higher $RR_{both\text{-}factors}$ (E) than the sum of $RR_{only\text{-}factor\text{-}1}$ and $RR_{only\text{-}factor\text{-}2}$ (D). $RR_{both\text{-}factors}$ is elevated after adjusting for gender, age, BMI, cooking oil, passive smoking, parent education degree, family income, family history of obesity, and family history of diabetes (adjusted model vs. unadjusted model).

Supervision. **Zhijun Zeng:** Investigation, Writing - review & editing. **Machteld N. Hylkema:** Writing - review & editing. **Zongwei Cai:** Writing - review & editing. **Xia Huo:** Supervision, Funding acquisition, Project administration.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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