Environment International 164 (2022) 107259

Contents lists available at ScienceDirect

Environment International

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

Full length article

Longitudinal relationships of polycyclic aromatic hydrocarbons exposure and genetic susceptibility with blood lipid profiles

Jixuan Ma [a,c,1], Xingjie Hao [b,1], Xiuquan Nie [a,c], Shijie Yang [a,c], Min Zhou [a,c], Dongming Wang [a,c], Bin Wang [a,c], Man Cheng [a,c], Zi Ye [a,c], Yujia Xie [a,c], Chaolong Wang [b,*], Weihong Chen [a,c,*]

[a] Department of Occupational & Environmental Health, School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei 430030, China

[b] Department of Epidemiology & Statistics, School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei 430030, China

[c] Key Laboratory of Environment and Health, Ministry of Education & Ministry of Environmental Protection, and State Key Laboratory of Environmental Health (Incubating), School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei 430030, China

ARTICLE INFO

Handling Editor: Adrian Covaci

Keywords:
Polycyclic aromatic hydrocarbons
Blood lipid
Polygenic risk scores
Genetic susceptibility

ABSTRACT

Objective: We aim to analyze the effects of polycyclic aromatic hydrocarbons (PAHs) exposure and genetic predisposition on blood lipid through a longitudinal epidemiological study.

Methods: We enrolled 4,356 observations who participated at baseline (n = 2,435) and 6-year follow-up (n = 1,921) from Wuhan-Zhuhai cohort. Ten urinary PAHs metabolites and blood lipid (*i.e.*, total cholesterol [TC], triglycerides [TG], low-density lipoprotein cholesterol [LDL-C], and high-density lipoprotein cholesterol [HDL-C]) were measured at both baseline and follow-up. The polygenic risk scores (PRS) of blood lipid were constructed by the corresponding genome-wide association studies. Linear mixed models were fit to identify associations between urinary PAHs metabolites, blood lipid, and lipid-PRSs in the repeated-measure analysis. Besides, longitudinal relationships of blood lipid with urinary PAHs metabolites and respective lipid-PRSs were examined by using linear regression models.

Results: Compared with subjects who had persistently low urinary total hydroxyphenanthrene (ΣOHPh), those with persistently high levels had an average increase of 0.137 mmol/l for TC and 0.129 mmol/l for LDL-C over 6 years. Each 1-unit increase of TC-, TG-, LDL-C-, and HDL-C-specific PRS were associated with an average increase of 0.438 mmol/l for TC, 0.264 mmol/l for TG, 0.198 mmol/l for LDL-C, and 0.043 mmol/l for HDL-C over 6 years, respectively. Compared with subjects who had low genetic risk and persistently low ΣOHPh, subjects with high LDL-specific PRS and persistently high ΣOHPh had an average increase of 0.652 mmol/l for LDL-C.

Conclusions: Our results suggest that high-level ΣOHPh exposure is associated with an average increase of LDL-C over 6 years, and those relationships can be aggravated by a higher LDL-C-genetic risk. No significant relationships were observed between other PAHs metabolites (including hydroxynaphthalene, hydroxyfluorene, and hydroxypyrene) and blood lipid changes over 6 years. Our findings emphasize the importance of preventing PAHs exposure, particularly among those with a higher genetic predisposition of hyperlipidemia.

1. Introduction

Dyslipidemia including the elevated total cholesterol (TC), triglycerides (TG), low-density lipoprotein-cholesterol (LDL-C), and reduced high-density lipoprotein cholesterol (HDL-C) are well-known risk factors for cardiovascular disease (CVD) and coronary artery disease (CAD) (Castelli 1988; Reiner 2017). Despite numerous clinical trials have documented the impact of pharmacologic interventions on

* Corresponding authors at: Department of Occupational & Environmental Health, School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei 430030, China (W. Chen), Department of Epidemiology & Statistics, School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei 430030, China (C. Wang).

E-mail addresses: chaolong@hust.edu.cn (C. Wang), wchen@mails.tjmu.edu.cn (W. Chen).

[1] These authors contribute equally to this work.

https://doi.org/10.1016/j.envint.2022.107259
Received 3 October 2021; Received in revised form 22 March 2022; Accepted 20 April 2022
Available online 25 April 2022

reducing blood lipid (Baigent et al., 2005; Cahalin et al., 2014), the prevalence of dyslipidemias is still high and increasing worldwide, especially in China (Cahalin et al., 2014; Yang et al., 2018; Ma et al., 2019). From a national report in 2018, the prevalence of dyslipidemias in Chinese adults has increased from 18.6% in 2002 to 40.4% in 2012, and this increase of dyslipidemia incidence will increase by approximately 9.2 million cases of cardiovascular events in China between 2010 and 2030 (Liu et al., 2019; Xi et al., 2020). Accumulating evidences suggested that environmental factors including environmental pollutants, unreasonable diet, lacking of physical activity, smoking, and alcohol intake were well recognized as major determinants for lipoprotein secretion and metabolism (Ellison et al., 2004; Cole et al., 2015), but recent studies also indicated that 40 to 60% of variation in plasma lipid was actually attributed to genetic factors (Namboodiri et al., 1985; Yu et al., 2005; Cole et al., 2015; Lu et al., 2016). All information indicates that both environmental and genetic factors may influence lipid metabolism and cause dyslipidemia. Clarifying the role or interactions of environmental factors with genetic variants on dyslipidemias may helpful for preventing blood lipid-related diseases including CVD and CAD (Cole et al., 2015).

Polycyclic aromatic hydrocarbons (PAHs) are a group of environmental pollutants that consist of two or more fused benzene rings and are regularly generated during incomplete combustion or pyrolysis of organic matters (Kim et al., 2013). In the general population, humans can be exposed to PAHs through indoor air (*e.g.*, tobacco smoke, and cooking) and outdoor air pollution (*e.g.*, burning of coal and wood and vehicle exhausts), but predominantly through smoked/grilled foods (Ma and Harrad 2015; Gao et al., 2018). However, it is worth noting that the workplace remains a major source of PAHs exposure, and several industries entailing high exposure to mixtures of PAHs are known or suspected carcinogens to humans (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans 2010; Barul and Parent 2021). Due to its high mobility, strong toxicity, and ability to bioaccumulation, exposure to PAHs has been associated with adverse health effects and continues to be an important public health issue worldwide (Kim et al., 2013; Yang et al., 2017). Recent experimental studies have suggested that exposure to PAHs can significantly impair lipid metabolism and induce blood lipid elevation in mice (Kawano et al., 2010; Jin et al., 2014; Li et al., 2019). However, epidemiological evidences on the impact of PAHs exposure on lipid metabolites are rarely reported. Our previous study found that exposure to PAHs was positively associated with dyslipidemia in general adults through a cross-sectional analysis (Ma et al., 2019). However, the longitudinal associations between PAHs exposure and altered blood lipid has not been reported to date.

Genome-wide association studies (GWASs) have successfully identified over 250 genetic loci associated with blood lipid, while these single variants typically have small effects and only explain a small fraction of the heritability, meaning that each single variant has limited predictive power (Do et al., 2013; Willer et al., 2013; Peloso et al., 2014; Cole et al., 2015; Spracklen et al., 2017). Polygenic risk score (PRS) of lipid, which combines effects of a large number of genetic variants, may contribute substantially to the risk of dyslipidemias and effectively stratify the high-risk populations (Cole et al., 2015). Previous lipid-PRSs have shown strong association with their corresponding lipid levels (Tikkanen et al., 2011; Do et al., 2013). However, most of them were constructed based on European ancestry populations, which might have poor predictive power in Chinese population due to the different genetic structures (Marquez-Luna et al., 2017; Lam et al., 2019; Martin et al., 2019). Particularly, the interaction effects of PAHs exposure with lipid-PRS on blood lipid levels remain unknown.

To fill these gaps, we repeatedly measured blood lipid profiles and urinary PAHs metabolites throughout 6 years from a Chinese cohort, and assessed longitudinal relationships of PAHs exposure with alteration of blood lipid. In addition, we generated lipid-PRSs for Chinese population based on GWAS summary statistics from Biobank Japan (BBJ), and evaluated potential interactions between PAHs metabolites and PRS on the longitudinal alteration of blood lipid.

2. Materials and Methods

2.1. Study Population

Participants included in the current analyses were from the Wuhan-Zhuhai cohort. The study design and population characteristics has been described in detail elsewhere (Song et al., 2014). Briefly, a total of 4,812 adult residents who lived in Wuhan or Zhuhai city for more than five years were enrolled between 2011 and 2012, and followed up every three years (*i.e.*, 2014–2015, and 2017–2018). All subjects completed an interviewer-administered questionnaire, underwent physical examinations, and provided blood and urine samples at each period. Because of lack of data on urinary PAHs metabolites in 2014–2015, we only analyzed data at baselines and 6-year follow-up (2017–2018 year) in this study. After excluding participants without data on urinary PAHs metabolites (n = 694), urinary creatinine (n = 3), blood lipid tests (n = 66), weight or height (n = 31) or genotyping data (n = 1,583), a total of 2,435 participants were included at baseline. Furthermore, we included 1,921 individuals with available data on blood lipid, urinary PAHs metabolites measurement, and genotyping after 6-years follow-up. Among them 1,427 subjects completed 2-time visits (visit both at baseline and follow-up). Taking together, a total of 2,929 subjects with 4,356 observations were included in the final analyses (Fig. S1). The comparison of baseline characteristics between the included and excluded participants was shown in Table S1.

All participants enrolled in this study provided written informed consent for participation, storage, and use of their blood or urine samples. This research protocol was approved by the Ethics and Human Subject Committee of Tongji Medical College, Huazhong University of Science and Technology.

2.2. Blood lipid Profiles

Fasting blood samples from individuals were stored in −80 ℃, and were thawed before assay. Serum concentrations of TC, TG, LDL-C, and HDL-C were measured in clinical labs by using blood biochemical analyzer according to the manufacturer instructions.

2.3. Urinary PAHs metabolites Concentrations

Spot urine sample was collected in the morning from each participant. We further extracted 3 ml of the urine sample to measure urinary PAHs metabolites. Detailed operation and laboratory protocols have been described previously (Li et al., 2012; Zhou et al., 2016; Nie et al., 2021). Briefly, ten detectable urinary PAHs metabolites, including 1-hydroxynaphthalene (1-OHNa), 2-hydroxynaphthalene (2-OHNa), 2-hydroxyfluorene (2-OHFlu), 9-hydroxyfluorene (9-OHFlu), 1- hydroxyphenanthrene (1-OHPh), 2-hydroxyphenanthrene (2-OHPh), 3-hydroxyphenanthrene (3-OHPh), 4-hydroxyphenanthrene (4-OHPh), 9 hydroxyphenanthrene (9-OHPh), and 1-hydroxypyrene (1-OHP) were determined by gas chromatography-mass spectrometry (GC–MS, Agilent Technologies, Santa, Clara, CA, USA). All valid urinary PAHs metabolites were corrected by the corresponding urinary creatinine (Cr) concentrations and presented as μg/mmol *Cr* for the further analyses. To assess exposure to each kind of PAHs, the sum concentrations of hydroxynaphthalene (ΣOHNa) = 1-OHNa + 2-OHNa, hydroxyfluorene (ΣOHFlu) = 2-OHFlu + 9-OHFlu; hydroxyphenanthrene (ΣOHPh) = 1-OHPh + 2-OHPh + 3-OHPh + 4-OHPh + 9-OHPh; and hydroxypyrene = 1-OHP were calculated, respectively. We selected those urinary hydroxylated metabolites, including naphthalene, fluorine, phenanthrene, and pyrene metabolites in the present study because of they were not only considered as priority hazardous pollutants by the U.S. Environmental Protection Agency (Hussar et al., 2012), but also could comprehensively reflect human exposure to PAHs from various sources

in environment (Zhou et al., 2016; Cao et al., 2020).

2.4. Covariates

Data on age (years), sex (male/female), ethnicity (Han, others), and education level (junior school or below, senior school, high school or above) were collected in a demographic questionnaire. At each study visit, information on cigarette smoking (smoker or not), alcohol consumption (drinker or not), passive smoke status (yes or not), physical activity (yes or not), and use of lipid-lowering drug (yes or not) were also collected. Body mass index (BMI) was calculated as weight (kg) divided by square of height (m). City was classified as Wuhan and Zhuhai city. Current smokers were defined as those who had smoked at least one cigarette per day in the past 6 months. Current drinkers were classified as subjects drinking at least once per week for over 6 months. Physical activity was defined as regularly doing at least 20 min per day of physical activity during leisure time over the previous 6 months (yes or no).

2.5. Genotyping and calculation of PRS

Genomic DNA was extracted from thawed whole blood samples with the Whole blood DNA Extraction Kit (Bioteke, Beijing, China). For each sample, DNA was loaded on Infinium OmniZhongHua-8 v1.3 BeadChip (Illumina, CA, USA) which contains > 890, 000 markers for genotyping, following the manufacturer's instructions. We then performed quality control (QC) of single nucleotide polymorphisms (SNPs) and samples using PLINK (v 2.0) (Chang et al., 2015), filtering SNPs with call rate < 0.95, minor allele frequencies (MAF) < 0.005, and Hardy Weinberg equilibrium (HWE) test $P < 10^{-6}$, removing samples with missing rate > 0.1, inbreeding coefficient < 5 standard deviations smaller than the mean, and the duplicated samples with genomic proportion of identical-by-descent$\hat{\pi} > 0.706$. Then the genotypes were phased with EAGLE2 (v2.3.5) (Loh et al., 2016) and imputed to the 1000 Genomes Project Phase III panel with Minimac4 (Genomes Project et al., 2015; Das et al., 2016). After removing variants with MAF < 0.005, imputation $R^2 < 0.3$, and HWE $P < 10^{-6}$, 8,923,692 autosomal variants were retained for the downstream analyses.

The PRSs of lipid (TC, TG, LDL-C, and HDL-C) were constructed based on GWAS summary statistics (*i.e.,* effect allele, beta, and *P* value for each SNP) from BBJ (https://jenger.riken.jp/en/result). We used the clumping and threshold (P + T) method implemented in the PRSice 2.0 program (Choi and O'Reilly 2019), where we set different thresholds for the association *P* value (5×10^{-8}, 5×10^{-7}, 5×10^{-6}, 5×10^{-5}, 5×10^{-4}, 5×10^{-3}, 5×10^{-2}, 5×10^{-1}, and 1) and clumped SNPs with LD $r^2 > 0.1$ within a 250 kb window. The PRS of i^{th} participant was calculated as:

$$PRS_i = \sum \beta_k X_{ik} \quad (1)$$

where β_k was the effect size of the variant k in BBJ, and X_{ik} was the number of effective alleles for SNP k ($X_{ik} = 0$, 1, or 2) of i^{th} participant in the present study.

2.6. Statistical analysis

Given the skewed-distributions of urinary PAHs metabolites and TG, we used log-transformed values to achieve approximately symmetrical distribution for the further analyses. Spearman's rank correlation analysis was used to calculate the correlations between each kind of urinary PAHs metabolites. In the repeated-measure design, we applied linear mixed models with subjects as a random effect to account for the linear associations between urinary PAHs metabolites and four blood lipid profiles. *P* values for trend were calculated using the tertile median value in our linear mixed models. The potential confounders in models were selected based on a priori knowledge about the risk factors for PAHs exposure and blood lipid (Hu et al., 2015; Ranjbar et al., 2015; Ma et al., 2019). Besides, we designed a directed acyclic graph (DAG) using the software DAGitty to identify minimal sufficient sets of covariates (Fig. S2). To correct for multiple testing, we calculated the corresponding false discovery rate (*FDR*)-adjusted *P* value by using Benjamini-Hochberg procedure. We additionally evaluated the associations between PRS and blood lipid profiles using linear mixed models after adjusting for age, ethnicity, sex, city, and the first 10 principal components of ancestry where appropriate. Here, the first 10 principal components representing the population structure were calculated with the approximate independent SNPs. In dose–response relationships analyses, PRS were categorized in to low (quintile 1), intermediate (quintile 2–4), and high (the quintile 5) genetic risk, as previously described (Jin et al., 2020). A potential non-linear association between PRS and four corresponding blood lipid profiles were assessed by integrating penalized splines in linear mixed models. In repeat-measure analysis, as TG was log-transformed, final results were reported as estimated percent changes with the 95% CIs, which were estimated as $(e^{\beta}\text{-}1) \times 100$ for each kind of urinary PAHs metabolites.

To estimate the effects of PAHs exposure on blood lipid over 6 years, we conducted a longitudinal analysis including 1,427 participants who participated both at enrollment and follow-up. The participants were divided into low or high exposure group according to the median value of total urinary PAHs metabolites. Then, participants were stratified into three groups as following: persistent low (urinary PAHs metabolites below the median at baseline and follow-up); inconsistent (urinary PAHs metabolites in different groups between baseline and follow-up); persistent high (urinary PAHs metabolites above the median at baseline and follow-up). Changes in blood lipid profiles were estimated as the difference between follow-up and baseline blood lipid profiles. And linear regression models were applied to estimate blood lipid changes over 6 years in the persistent high and inconsistent group, compared with the persistent low group.

We further evaluated the relationships between PRS and blood lipid changes over 6 years with linear models as previous described (Varga et al., 2014). Briefly, we included the follow-up lipid measure as the dependent variable and adjusted for age, ethnicity, sex, city, the first 10 principal components of ancestry where appropriate, and the respective trait's baseline value.

$$follow-up\ lipid = \alpha + \beta_{PRS} + \beta_{baseline\ lipid} + \beta_{cov_1} + \cdots + \beta_{cov_j} + \varepsilon \quad (2)$$

For the sake of simplicity, the estimates in the above model referred to changes in the responding blood lipid.

We further categorized subjects according to the PAHs exposure status (persistent high or low) and PRS levels (low/intermediate/high genetic risk), and investigated the joint effect of PAHs exposure and PRS on changes of blood lipid profiles over 6 year by using linear regression models. The multiplicative joint effect was evaluated by adding an interaction term of PAHs exposure status and PRS levels (continuous) to those models:

$$lipid\ change = \alpha + \beta_{PRS} + \beta_{PAHs\ exposure\ status} + \beta_{PAHs\ exposure\ status \times PRS} + \beta_{cov_1} + \cdots + \beta_{cov_j} + \varepsilon \quad (3)$$

All statistical analysis was performed with R software (version 3.4.1, R Foundation for Statistical Computing, Austria). *P* value < 0.05 was considered to be statistically significant. All *P* values were 2-sided.

3. Results

3.1. Characteristics of study population

The basic characteristics for the 4,356 observations are summarized in Table 1. Of them, 32.85% were male and 99.65% were Han race. The mean (SD) age and BMI of all subjects were 56.16 (11.47) years and

Table 1
Basic characteristics of all study observations ($n_{observations}$ = 4,356).

Characteristics	All observations	Subjects at baseline (2011–2012)	Subjects at follow-up (2017–2018)
Number of subjects, n	4356	2435	1921
Age, years (mean ± SD)	56.16 ± 11.47	54.15 ± 11.83	58.71 ± 10.47
BMI, kg/m^2 (mean ± SD)	24.51 ± 3.45	24.25 ± 3.41	24.84 ± 3.48
Height, cm (mean ± SD)	158.64 ± 7.86	158.91 ± 7.78	158.30 ± 7.94
Weight, kg (mean ± SD)	61.81 ± 10.58	61.35 ± 10.42	62.39 ± 10.74
Male, n (%)	1431 (32.85)	805 (33.06)	626 (32.59)
Han race, n (%)	4341 (99.65)	2420 (99.38)	1921 (100.00)
Smoker, n (%)	707 (16.23)	406 (16.67)	301 (15.67)
Drinker, n (%)	687 (15.77)	371 (15.24)	316 (16.45)
Regular physical activity, n (%)	2329 (53.47)	1229 (50.47)	1100 (57.26)
Education, n (%)			
Junior school or below	2931 (67.29)	1504 (61.77)	1427 (74.28)
Senior school	1169 (26.84)	679 (27.89)	490 (25.51)
High school or above	256 (5.87)	252 (10.35)	4 (0.21)
Family history of hyperlipidemias, n (%)	303 (6.95)	173 (7.10)	130 (6.77)
Use of lipid-lowing drugs, n (%)	589 (13.52)	449 (18.44)	140 (7.29)
Blood lipid parameters, mmol/l			
TC (mean ± SD)	5.10 ± 1.11	5.11 ± 1.11	5.08 ± 1.11
TG median (IQR)	1.24 (0.99)	1.20 (1.01)	1.29 (0.96)
LDL-C (mean ± SD)	3.07 ± 0.96	3.14 ± 1.01	2.99 ± 0.89
HDL-C (mean ± SD)	1.46 ± 0.40	1.55 ± 0.42	1.35 ± 0.34
Urinary PAHs metabolites, μg/mmol Cr, median (IQR)			
ΣOHNa	1.85 (1.83)	1.64 (1.66)	2.05 (2.02)
ΣOHFlu	0.72 (1.05)	1.14 (1.40)	0.38 (0.39)
ΣOHPh	1.37 (1.42)	1.67 (1.46)	0.94 (1.01)
ΣOHP	0.34 (0.73)	0.70 (0.76)	0.04 (0.09)

Abbreviations: BMI, body mass index; HDL-C, high density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low density lipoprotein cholesterol; SD, standard deviation; IQR, interquartile range; TC, total cholesterol; TG, triglyceride; PAH, polycyclic aromatic hydrocarbon; ΣOHNa, total concentration of hydroxynaphthalene; ΣOHFlu, total concentration of hydroxyfluorene; ΣOHPh, total concentration of hydroxyphenanthrene; ΣOHP, total concentration of hydroxypyrene.

24.51 (3.45) kg/m^2, respectively. More than four-fifths of subjects were non-smokers and non-drinkers. The distributions of four kinds of urinary PAHs metabolites for all participants are also shown in Table 1 and Table S2. The medians concentration (interquartile range) of ΣOHNa, ΣOHFlu, ΣOHPh, and ΣOHP were 1.85 (1.83), 0.72 (1.05), 1.37 (1.42), and 0.34 (0.73) μg/mmol *Cr*, respectively. Besides, four kinds of urinary PAHs metabolites had weak to strong correlations with each other (*r*: 0.22 to 0.86) and highest correlation was observed between urinary ΣOHFlu and ΣOHPh (Fig. S3). The subjects at follow-up were older, and the proportions of regular physical activity were higher than those at baseline. Besides, the concentrations of ΣOHFlu, ΣOHPh, and ΣOHP decreased while ΣOHNa increased at follow-up when compared with those at baseline (Table 1).

3.2. Associations between urinary PAHs metabolites and four blood lipid Profiles

In repeated-measure analyses, we found significant relationships between blood lipid profiles and urinary PAHs metabolites, which were analyzed as either continuous or categorical variables. In the continuous analyses, each 1-unit increase in log-transformed ΣOHFlu and ΣOHPh was associated with an average increase of 0.057 and 0.079 mmol/l for TC, respectively ($P < 0.05$, Table 2). In addition, each 1-unit increase in log-transformed ΣOHNa, ΣOHFlu, ΣOHPh, and ΣOHP was linked with

Table 2
The associations between urinary PAHs metabolites and blood lipid profiles in the repeated-measures ($n_{observations}$ = 4356).

Variables	Effect estimates by continuous metabolites	Effect estimates (95% CI) by tertiles of metabolites [c]			*P* for trend[b]	FDR
		Tertile 1	Tertile 2	Tertile 3		
ΣOHNa (μg/mmol Cr)						
TC	0.034 (-0.002, 0.070)	0 (Ref)	0.049 (-0.018, 0.115)	0.055 (-0.013, 0.124)	0.16	0.08
TG[a]	−0.167 (-1.995, 1.694)	0 (Ref)	−0.911 (-4.252, 2.548)	−0.911 (-4.252, 2.548)	0.96	0.86
LDL-C	0.072 (0.036, 0.108)	0 (Ref)	0.169 (0.101, 0.237)	0.155 (0.086, 0.224)	<0.05	<0.05
HDL-C	−0.004 (-0.018, 0.010)	0 (Ref)	0.011 (-0.015, 0.037)	−0.005 (-0.031, 0.022)	0.54	0.62
ΣOHFlu (μg/mmol Cr)						
TC	0.057 (0.032, 0.083)	0 (Ref)	0.088 (0.023, 0.152)	0.143 (0.078, 0.209)	<0.05	<0.05
TG[a]	−2.038 (-3.318, −0.740)	0 (Ref)	3.615 (0.209, 7.136)	−5.286 (-8.446, −2.017)	<0.05	<0.05
LDL-C	0.092 (0.066, 0.119)	0 (Ref)	0.157 (0.090, 0.223)	0.240 (0.173, 0.308)	<0.05	<0.05
HDL-C	0.059 (0.049, 0.069)	0 (Ref)	0.087 (0.062, 0.112)	0.158 (0.133, 0.184)	<0.05	<0.05
ΣOHPh (μg/mmol Cr)						
TC	0.079 (0.047, 0.112)	0 (Ref)	0.171 (0.105, 0.236)	0.146 (0.078, 0.214)	<0.05	<0.05
TG[a]	−0.274 (-1.951, 1.432)	0 (Ref)	0.749 (-2.633, 4.249)	−1.581 (-4.992, 1.953)	0.29	0.81
LDL-C	0.114 (0.080, 0.147)	0 (Ref)	0.253 (0.186, 0.320)	0.233 (0.165, 0.302)	<0.05	<0.05
HDL-C	0.058 (0.045, 0.071)	0 (Ref)	0.107 (0.082, 0.133)	0.132 (0.106, 0.158)	<0.05	<0.05
ΣOHP (μg/mmol Cr)						
TC	0.011 (-0.004, 0.027)	0 (Ref)	0.062 (-0.004, 0.127)	0.030 (-0.035, 0.094)	0.61	0.18
TG[a]	−1.095 (-1.886, −0.297)	0 (Ref)	−2.395 (-5.631, 0.952)	−4.194 (-7.315, −0.968)	0.01	0.02
LDL-C	0.025 (0.009, 0.041)	0 (Ref)	−0.021 (-0.089, 0.047)	0.088 (0.020, 0.155)	<0.05	<0.05
HDL-C	0.044 (0.038, 0.050)	0 (Ref)	0.115 (0.090, 0.140)	0.177 (0.152, 0.201)	<0.05	<0.05

Abbreviations: HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride; PAH, polycyclic aromatic hydrocarbon; ΣOHNa, total concentration of hydroxynaphthalene; ΣOHFlu, total concentration of hydroxyfluorene; ΣOHPh, total concentration of hydroxyphenanthrene; ΣOHP, total concentration of hydroxypyrene.
Linear mixed models with a subject-specific random intercept were used to examine the dose–response associations between urinary PAHs metabolites and blood lipid parameters after adjusting for age, BMI, sex, city, ethnicity, education, smoking status, drinking status, passive smoking status, physical activity, family history of hyperlipidemias, and use of lipid-lowering drug.
[a] TG was log-transformed in the models and the results shown as percent change (95% CI).

[b] *P* for trend were calculated using the tertile median value in the linear mixed models.

[c] The cut-off value for the tertiles of urinary PAHs metabolites were (<1.37, 1.37–2.47, >2.47) for ΣOHNa; (<0.46, 0.46–1.08, >1.08) for ΣOHFlu; (<0.99, 0.99–1.82, >1.82) for ΣOHPh; (<0.11, 0.11–0.60, >0.60) for ΣOHP.

an average increase of 0.072, 0.092, 0.114, and 0.025 mmol/l for LDL-C, respectively ($P < 0.05$, Table 2). Each 1-unit increase in log-transformed ΣOHFlu, ΣOHPh, and ΣOHP was related to an average increase of 0.059, 0.058 and 0.044 mmol/l for HDL-C, respectively ($P < 0.05$, Table 2). Each 1-unit increase in log-transformed ΣOHFlu and ΣOHP was associated with an average decrease of 2.038% and 1.095% for TG, respectively. In categorical analysis, significantly monotonic LDL-C and HDL-C increase were observed for urinary ΣOHFlu and ΣOHPh (all *P* for trend < 0.05, Table 2). Besides, the above relationships remained the same after correcting for multiple tests (Table 2).

3.3. Associations between PRS and four blood lipid Profiles

Nine PRSs based on different *P* value thresholds were built for each lipid trait and showed highly significant associations with their corresponding lipid trait in repeated-measures analyses (Table S3). In particular, PRSs derived from 101 SNPs for TC, 104 SNPs for TG, 69 SNPs for LDL-C, and 163 SNPs for HDL-C at $P < 5 \times 10^{-8}$ (threshold) had the strongest association with their corresponding blood lipid trait (Table S3). Thus, we used those PRSs to represent the genetic risks of blood lipid trait for further analyses. In addition, bioinformatics results showed that those SNPs variability involved in PRS might participant in regulation of lipid-related genes including DOCK7, LDLR, APOE, and PCSK9 (Table S4-7).

We found that 1-unit increase of the TC-, LDL-C-, and HDL-C-specific PRS were associated with an average increase of 0.691 mmol/l for TC, 0.457 mmol/l for LDL-C, or 0.117 mmol/l for HDL-C, respectively (all $P_{overall} < 0.05$, $P_{nonlinear} > 0.05$, Table 3, Figure S4). Each 1-unit increase of TG-specific PRS was linked with an average increase of 31.363 % for TG. Compared with subjects who had low PRSs, participants with high PRSs had significantly average increases of TC (β: 0.549, 95% CIs: 0.438–0.659), TG (47.181%, 38.574% – 56.323%), LDL-C (0.395, 0.300–0.491), and HDL-C (0.218, 0.177–0.258), respectively (Table 3).

Table 3
Associations between four blood lipid profiles and the PRSs in repeated-measures ($n_{observations} = 4356$).

Variables[a]	Effect estimates by continuous PRS	Effect estimates (95% CI) by categorization of PRS[b]			*P* for trend
		Low score	Intermediate score	High score	
TC	0.691 (0.568, 0.814)	0 (Ref)	0.256 (0.165, 0.347)	0.549 (0.438, 0.659)	<0.05
TG[c]	31.363 (26.492, 36.422)	0 (Ref)	14.721 (9.177, 20.545)	47.181 (38.574, 56.323)	<0.05
LDL-C	0.457 (0.366, 0.548)	0 (Ref)	0.193 (0.117, 0.273)	0.395 (0.300, 0.491)	<0.05
HDL-C	0.117 (0.098, 0.136)	0 (Ref)	0.097 (0.064, 0.130)	0.218 (0.177, 0.258)	<0.05

Abbreviations: CI, confidence interval; HDL-C, high density lipoprotein cholesterol; PRS, polygenic risk score; LDL-C, low density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride.

[a] Linear mixed models were used to assess the relationships between PRS and four blood lipid with adjustment for age, sex, city, ethnicity, and the first 10 principal components of ancestry.

[b] Defined by quantiles of PRS: low (the bottom quintile), intermediate (quintiles 2–3) and high (the top quintile). The cut-off value was (<0.33, 0.33–0.81, >0.81) for TC-PRS; (<-0.93, [-0.93, −0.1], >-0.1) for TG-PRS; (<0.58, 0.58–1.12, >1.12) for LDL-C-PRS; (<-0.52, −0.52–0.59, >0.59) for HDL-C-PRS, respectively.

[c] TG was log-transformed in the models and the results shown as percent change (95% CI).

3.4. Longitudinal analysis of urinary PAHs metabolites and changes in blood Lipid

A longitudinal analysis was conducted to quantify the relationship of urinary PAHs metabolites with change of blood lipid over 6 years (Table 4). Compared with subjects who had persistently low exposure, those with persistently high levels of urinary ΣOHPh had an average increase of 0.137 mmol/l for TC and 0.129 mmol/l for LDL-C, respectively over 6 years. No significant relationships were observed between urinary ΣOHNa, ΣOHFlu, or ΣOHP and four lipid profiles changes over 6 years (all $P > 0.05$, Table 4).

3.5. Longitudinal analysis of PRSs and changes in blood Lipid.

The PRSs were strongly associated with the change of their corresponding blood lipid trait in longitudinal analyses of 6 years (Table 5).

Table 4
Estimates changes of blood lipid over 6 years associated with urinary PAHs metabolites (n = 1427).

Variables	Effect estimates (95% CI) in blood lipid over 6 years		
	Persistent low	Inconsistent	Persistent high
ΣOHNa (μg/mmol Cr)			
TC change	0 (Ref)	0.008 (-0.103, 0.119)	−0.028 (-0.152, 0.097)
TG change	0 (Ref)	−0.107 (-0.254, 0.041)	−0.100 (-0.265, 0.065)
LDL-C change	0 (Ref)	0.014 (-0.097, 0.126)	0.072 (-0.053, 0.197)
HDL-C change	0 (Ref)	0.013 (-0.032, 0.057)	0.008 (-0.042, 0.058)
ΣOHFlu (μg/mmol Cr)			
TC change	0 (Ref)	0.090 (-0.020, 0.201)	0.091 (-0.036, 0.217)
TG change	0 (Ref)	−0.071 (-0.217, 0.075)	0.141 (-0.026, 0.308)
LDL-C change	0 (Ref)	0.056 (-0.055, 0.167)	0.048 (-0.079, 0.175)
HDL-C change	0 (Ref)	−0.014 (-0.058, 0.031)	−0.004 (-0.055, 0.047)
ΣOHPh (μg/mmol Cr)			
TC change	0 (Ref)	0.068 (-0.043, 0.180)	0.137 (0.009, 0.266)
TG change	0 (Ref)	0.104 (-0.044, 0.252)	−0.004 (-0.174, 0.167)
LDL-C change	0 (Ref)	0.058 (-0.054, 0.170)	0.129 (0.001, 0.259)
HDL-C change	0 (Ref)	−0.006 (-0.051, 0.039)	−0.035 (-0.087, 0.017)
ΣOHP (μg/mmol Cr)			
TC change	0 (Ref)	−0.027 (-0.138, 0.085)	0.042 (-0.085, 0.169)
TG change	0 (Ref)	−0.078 (-0.226, 0.070)	−0.085 (-0.253, 0.083)
LDL-C change	0 (Ref)	−0.048 (-0.160, 0.064)	−0.062 (-0.189, 0.065)
HDL-C change	0 (Ref)	0.026 (-0.019, 0.070)	0.014 (-0.037, 0.065)

Abbreviations: HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride; PAH, polycyclic aromatic hydrocarbon; ΣOHNa, total concentration of hydroxynaphthalene; ΣOHFlu, total concentration of hydroxyfluorene; ΣOHPh, total concentration of hydroxyphenanthrene; ΣOHP, total concentration of hydroxypyrene. All models adjusted for age, BMI, sex, city, ethnicity, education, smoking status, drinking status, passive smoking status, physical activity, family history of hyperlipidemias, and use of lipid-lowering drug.

Table 5
Blood lipid levels changes (95% CI) over 6 follow-up by PRS.

Variables[a]	Effect estimates by continuous PRS	Effect estimates (95% CI) by categorization of PRS[b]			*P* for trend
		Low score	Intermediate score	High score	
TC change	0.438 (0.285, 0.592)	0 (Ref)	0.177 (0.067, 0.286)	0.428 (0.292, 0.564)	< 0.05
TG change	0.264 (0.174, 0.354)	0 (Ref)	0.139 (0.023, 0.255)	0.335 (0.192, 0.478)	< 0.05
LDL-C change	0.198 (0.083, 0.313)	0 (Ref)	0.058 (-0.038, 0.154)	0.184 (0.066, 0.302)	< 0.05
HDL-C change	0.043 (0.021, 0.065)	0 (Ref)	0.024 (-0.013, 0.060)	0.083 (0.037, 0.128)	< 0.05

Abbreviations: CI, confidence interval; HDL-C, high density lipoprotein cholesterol; PRS, polygenic risk score; LDL-C, low density lipoprotein cholesterol; TG, triglyceride; TC, total cholesterol.

[a] Linear regression models were used to examine the dose–response associations between the selected polygenic risk score and blood lipid parameters after adjusting for age, sex, city, ethnicity, and the first 10 principal components of ancestry where appropriate.

[b] Defined by quantiles of PRS: low (the bottom quintile), intermediate (quintiles 2–3) and high (the top quintile). The cut-off value was (<0.33, 0.33–0.80, >0.80) for TC-PRS; (<-0.93, [-0.93, −0.11], >-0.11) for TG-PRS; (<0.57, 0.57–1.11, >1.11) for LDL-C-PRS; (<-0.52, −0.52–0.58, >0.598) for HDL-C-PRS, respectively.

Each 1-unit increase of the TC-, TG-, LDL-C-, and HDL-C-specific PRS were associated with an average increase of 0.438 mmol/l for TC, 0.264 mmol/l for TG, 0.198 mmol/l for LDL-C or 0.043 mmol/l for HDL-C, respectively over 6 years. When compared with those in low genetic risk (the first quintile of lipid-PRS), participants with high genetic risk (the fifth quintile of lipid-PRS) had a significantly average increase of TC (0.428, 0.292–0.564), TG (0.335, 0.192–0.478), LDL-C (0.184, 0.066–0.302), and HDL-C (0.083, 0.037–0.128), respectively (Table 5).

3.6. Combined effects of ΣOHPh exposure and genetic risk on the blood lipid Changes

We further tested whether there was interaction between urinary PAHs metabolites exposure and the genetic risk on blood lipid changes over 6 years. Since the interaction effects were only observed between ΣOHPh and LDL-C-specific PRS on LDL-C changes (*P* for interaction < 0.05), we further assessed their joint effects by the stratified analysis. After stratifying participants by PRSs (low, intermediate and high), we observed the cumulative joint effects of ΣOHPh exposure and genetic risk on the changes in LDL-C over 6 years (Fig. 1). Compared with those had low genetic risk and persistently low ΣOHPh exposure, participants with high LDL-specific PRS and persistently high exposure levels of ΣOHPh had an average increase of 0.652 mmol/l for LDL-C over 6 years.

4. Discussion

In this prospective cohort study, significant positive relationships between urinary PAHs metabolites and blood lipid profiles were observed through cross-sectional and longitudinal analysis. In particular, persistently high exposure of urinary ΣOHPh was associated with an average increase of TC or LDL-C over 6 years. No significant relationships were observed between other metabolites (ΣOHNa, ΣOHFlu, and ΣOHP) and four lipid profiles changes over 6 years. We continued to evaluate the effects of genetic factors on blood lipid, and the combined effects of PAHs exposure and genetic factors on blood lipid. By constructing the PRS based on the overall genetic effects of the risk alleles of lipid traits, we found strong positive associations between each PRS and its corresponding traits, and the associations of PRS with the elevation of blood lipid profiles remained robust after 6 years of follow-up. Interaction analyses further showed that genetic susceptibility could aggravate the associations between ΣOHPh exposure and LDL-C increase.

Our findings have substantial public health implications. First, PAHs is a group of widespread environmental pollutants, and its health damage is receiving great attention. The adverse effects of exposure to high levels of PAHs on blood lipid is still lack of follow-up study in relatively large-scale populations. Our results suggested that persistently PAHs exposure was detrimental to the dyslipidemias, which might emphasize an urgent need to control or restrict PAHs exposure from various sources. Besides, the results from gene-environmental interaction analyses in this study indicated that adults who had persistently high PAHs exposure and higher lipid-PRS could be more susceptible to hyperlipidemias, which might facilitate the emergence of new strategies for personalized precision prevention of hyperlipidemias.

Biomonitoring can provide an aggregate exposure estimate, integrating exposures from all sources, especially those that are hard to measure, such as skin exposure or hand to mouth transfer *et al.* (Thai

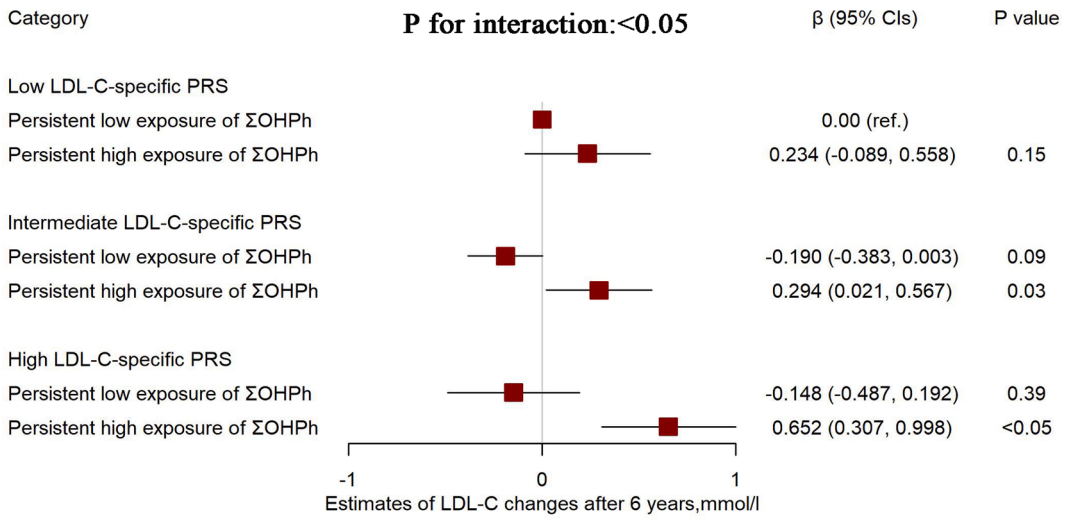

Fig. 1. The joint effects between urinary PAHs metabolites and PRS on blood lipid changes over 6 years (n = 1427). Abbreviations: CI, confidence interval; PRS, polygenic risk score; LDL-C, low density lipoprotein cholesterol. All models adjusted for age, BMI, sex, city, ethnicity, education, smoking status, drinking status, passive smoking status, physical activity, family history of hyperlipidemias, and use of lipid-lowering drug.

et al., 2016). In this study, we used these four reliable urinary PAHs markers to assess exposure, which not only could accurately reflect PAHs exposure levels but also reflect PAHs exposure from all possible sources. For instance, our previous study suggested that among this population, cigarette smoking had the greatest contribution to ΣOHNa, and higher dietary intake was associated with urinary levels of ΣOHNa and ΣOHFlu (Cao et al., 2020); traffic exposure was found to have a greater contribution to urinary levels of ΣOHFlu and ΣOHPh (Cao et al., 2020). On the other hand, each kind of PAHs had different structures and specific adverse effects. Assessing their health effects separately might contribute to a better knowledge on the impact of PAHs components exposure.

Epidemiological evidences for effects of PAHs exposure on blood lipid have been growing in recent years, but the conclusions are not always consistent. Similar to our results, Ranjbar et al. conducted a cross-sectional study enrolled 4,765 U.S. adults, and observed that several PAH metabolites (including OHNa, OHFlu, OHPh, OHP, except for 1-OHPh) were positively associated in a dose-dependent manner with the dyslipidemia risk (Ranjbar et al., 2015). Likewise, a study enrolled of 1,878 American nondiabetic adults conducted by Hu et al. also suggested a negative relationship of urinary PAHs metabolites with TG (Hu et al., 2015). Specifically, increased 3-OHFlu and 1-OHP were negatively related to TG, but they did not observe any significant relationships of OHNa and OHPh with TG. In our previous study, we used baseline data from Wuhan-Zhuhai cohort and showed that elevated urinary PAHs metabolites were positively associated with TC and LDL-C (Ma et al., 2019), which was in line with the results from the repeated-measure analyses in the present study. Nevertheless, one natural experiment studied 26 healthy young adults who traveled from less-polluted Los Angeles to more-polluted Beijing, and reported that blood lipid did not change significantly during the travel period and were not associated with urinary OH-PAHs concentrations (Lin et al., 2019). The differences in study design, sample size, ethnicity, and especially in variations in PAHs exposure levels may have contributed to the inconsistent results. The median of urinary ΣOH-PAHs was 51.29 mg/L (4.74 mg/mmol *Cr*) in the present study. This exposure levels were similar with pregnant women in the same city, but was significantly higher than those in other populations, such as in US (median: 5.493 mg/L), Malaysia (median: 2.26 mg/L), Japan (median: 4.03 mg/L), and India (median: 6.75 mg/L) (Cao et al., 2020).

Our longitudinal analyses suggested that persistently high exposure to ΣOHPh was positively associated with increased TC or LDL-C over 6 years, which might provide additional evidences to support a causal role of PAHs exposure in the elevation of blood lipid levels. Besides, null longitudinal relationships were also observed between urinary ΣOHNa, ΣOHFlu, or ΣOHP and four lipid profiles changes over 6 years. We cannot explain the exact reasons for above confusing results. Perhaps their low stability limited the ability to assess their long-term toxic effects. For example, published literature indicated that health studies with a single urinary 1-naphthol measurement would have non-differential exposure misclassification, which would tend to bias results towards the null and limit the ability to detect an association between the health outcome and 1-naphthol (Dobraca et al., 2018). However, further studies are still encouraged to prove our speculation.

The biological plausibility that PAHs exposure increases blood lipid is supported by experimental studies, although the underlying mechanisms are not fully understood. Previous *in vivo* and *in vitro* studies have revealed that PAHs could active arylhydrocarbon receptor (AhR) signaling pathway, which enables PAHs to be metabolized by cytochrome P450 and generate harmful reactive oxygen species (ROS) (Ramesh et al., 2002; Vogel et al., 2020). PAHs metabolites and excessive ROS can attack lipid, causing oxidation reactions of lipid and dysregulation of lipid metabolism, which ultimately could promote the process of dyslipidemias occurrence (Penning et al., 1996; Bonvallot et al., 2001; Hayashi and Cortopassi 2015; Li et al., 2019).

Large-scale genetic association analyses have increasingly identified the SNPs associated with lipid, while single variant typically has a small effect and correspond to a small fraction of the heritability (Kathiresan et al., 2009; Teslovich et al., 2010; Do et al., 2013; Willer et al., 2013; Peloso et al., 2014; Spracklen et al., 2017). Using expanded sets of lipid-associated SNPs (e.g., PRS) have an improved discrimination for blood lipid and incident dyslipidemias (Murray et al., 2009; Lu et al., 2016; Dron and Hegele 2019). In our study, we developed four new lipid-PRSs derived from over 100 SNPs identified in large-scale GWAS studies from BBJ, and observed strong associations between each PRS and their respective phenotypes in the participants of our study. Perhaps the large number of SNPs identified by well-powered GWAS, which span across many candidate genes encoding diverse proteins, have contributed to the robust relationships.

It has been well recognized that approximately 40 to 60% of variation in blood lipid is genetically based (Namboodiri et al., 1985; Yu et al., 2005), but those identified loci only can account for $< 12\%$ of variation in each of these lipid traits (Teslovich et al., 2010; Asselbergs et al., 2012; Willer et al., 2013). These findings suggested that environmental factors are important determinants of lipoprotein secretion and metabolism in addition to genetics. Interaction effects of dietary intake, physical activity or smoking with genetic predisposition on blood lipid have been proved in previous literatures (Bernstein et al., 2002; Burneiko et al., 2006; Miao et al., 2012; Brahe et al., 2013; Bentley et al., 2019; Hannon et al., 2020). But interactions between genetic risk and PAHs exposure on lipid metabolism is largely unknown. To our knowledge, this is the first study to show a positive interaction of PAHs exposure with genetic components on the increased blood lipid, which promoted new insights on the pathological mechanism of blood lipid metabolism and abnormalities. Perhaps variants that affects gene expression of DOCK7, LDLR, APOE, and PCSK9, which were included in our PRS, might subsequently regulate the inflammatory response or ROS generation (Miyake et al., 2000; Licastro et al., 2007; Tang et al., 2019; Mbikay et al., 2020). Further experimental studies are needed to understand the underlying mechanism.

Our study has several strengths. First, we assessed the effects of PAHs exposure on blood lipid using longitudinal analysis, and exploratory provided evidences on the modifying effect of genetic predisposition on relationships between PAHs exposure and elevation of blood lipid in a relatively large population. Second, we used a large prospective cohort with repeated-measures, allowing us to account for within-subject variability and provides robust results for the relationships between urinary PAHs metabolites, lipid-PRSs, and blood lipid. Third, we had very adequately sample size to achieve high levels of statistical power and reduce the chance for making the type II error. We assessed the statistical power for each model, and observed that the statistical power for all models were over 90%. Besides, the sample size was$>$100 events for each predictor parameter in our study, which further indicated that the sample size was suitable in the regression analysis (Riley et al., 2020). Nevertheless, several limitations need also to be discussed. First, the PRS of lipids in our Chinese cohort was constructed by using the public available GWAS summary statistics from BBJ due to its similarity to Chinese population, while the East Asian specific PRS might not be generalizable to other populations. Second, the low risk of selection bias caused by the missing data might occur in this study. However, we noted that the levels of exposure (urinary PAHs metabolites) and outcomes (blood lipid) variables did not significantly vary between included and excluded subjects. Besides, we adjusted potential confounders among included subjects in the main analyses, which could provide more reliable estimates. Third, using single pollutant models to assess their toxic effects on blood lipid, which ignored the interference of other PAHs metabolites and might confound our results. Fourth, using single spot urine samples to evaluate the levels of PAHs exposure might not consider their possible variability overtime. Biomonitoring studies have suggested that the reliability of spot urine measurements for PAHs seems to be poor to moderate (Dobraca et al., 2018; Patel et al., 2021). While, the exposure routes of PAHs in our study are thought to be relatively

stable. These community participants had stable dietary pattern, smoking status, and travel model, especially without high occupational PAHs exposure. Finally, some degree of residual confounding is still possible despite a relatively comprehensive adjustment of demographic and lifestyle factors.

5. Conclusion

In this study, we observed that ΣOHPh exposure were positively associated with an average increase of TC or LDL-C over 6 years. Besides, we found that the positive relationships between ΣOHPh and LDL-C could be aggravated by a higher lipid-genetic risk. No significant relationships were observed between other metabolites (ΣOHNa, ΣOHFlu, and ΣOHP) and four lipid profiles changes over 6 years. Our findings provide new insight into personalized prevention and interventions for dyslipidemias, and further emphasize the importance of preventing PAHs exposure, particularly among those with a higher genetic predisposition of hyperlipidemia.

CRediT authorship contribution statement

Jixuan Ma: Conceptualization, Funding acquisition, Formal analysis, Investigation, Methodology, Writing – original draft. **Xingjie Hao:** Conceptualization, Funding acquisition, Formal analysis, Investigation, Methodology, Writing – original draft. **Xiuquan Nie:** Investigation, Methodology. **Shijie Yang:** Investigation. **Min Zhou:** Investigation, Data curation. **Dongming Wang:** Investigation. **Bin Wang:** Investigation. **Man Cheng:** Investigation. **Zi Ye:** Investigation. **Yujia Xie:** Investigation. **Chaolong Wang:** Conceptualization, Methodology, Formal analysis, Supervision, Writing – review & editing. **Weihong Chen:** Conceptualization, Funding acquisition, Investigation, Data curation, Writing – review & editing, Supervision.

Declaration of Competing Interest

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

Acknowledgements

The authors thank all the participants of the study.

Funding source

This work was supported by the Key Program of the National Natural Science Foundation of China [grant number 91543207]; the Major Research Program of the National Natural Science Foundation of China [grant number 91843302]; the China Postdoctoral Science Foundation [grant number 2019M652656]; the National Natural Science Foundation of China [grant number 82003561].

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2022.107259.

References

Asselbergs, F.W., Guo, Y., van Iperen, E.P., Sivapalaratnam, S., Tragante, V., Lanktree, M. B., et al., 2012. Large-scale gene-centric meta-analysis across 32 studies identifies multiple lipid loci. Am. J. Hum. Genet. 91, 823–838. https://doi.org/10.1016/j.ajhg.2012.08.032.

Baigent, C., Keech, A., Kearney, P.M., Blackwell, L., Buck, G., Pollicino, C., et al., 2005. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet 366, 1267–1278. https://doi.org/10.1016/S0140-6736(05)67394-1.

Barul, C., Parent, M.E., 2021. Occupational exposure to polycyclic aromatic hydrocarbons and risk of prostate cancer. Environ. Health 20, 71. https://doi.org/10.1186/s12940-021-00751-w.

Bentley, A.R., Sung, Y.J., Brown, M.R., Winkler, T.W., Kraja, A.T., Ntalla, I., et al., 2019. Multi-ancestry genome-wide gene-smoking interaction study of 387,272 individuals identifies new loci associated with serum lipids. Nat. Genet. 51, 636–648. https://doi.org/10.1038/s41588-019-0378-y.

Bernstein, M.S., Costanza, M.C., James, R.W., Morris, M.A., Cambien, F., Raoux, S., et al., 2002. Physical activity may modulate effects of ApoE genotype on lipid profile. Arterioscler. Thromb. Vasc. Biol. 22, 133–140. https://doi.org/10.1161/hq0102.101819.

Bonvallot, V., Baeza-Squiban, A., Baulig, A., Brulant, S., Boland, S., Muzeau, F., Barouki, R., Marano, F., 2001. Organic compounds from diesel exhaust particles elicit a proinflammatory response in human airway epithelial cells and induce cytochrome p450 1A1 expression. Am. J. Respir. Cell Mol. Biol. 25 (4), 515–521. https://doi.org/10.1165/ajrcmb.25.4.4515.

Brahe, L.K., Ängquist, L., Larsen, L.H., Vimaleswaran, K.S., Hager, J., Viguerie, N., Loos, R.J.F., Handjieva-Darlenska, T., Jebb, S.A., Hlavaty, P., Larsen, T.M., Martinez, J.A., Papadaki, A., Pfeiffer, A.F.H., van Baak, M.A., Sørensen, T.I.A., Holst, C., Langin, D., Astrup, A., Saris, W.H.M., 2013. Influence of SNPs in nutrient-sensitive candidate genes and gene-diet interactions on blood lipids: the DiOGenes study. Br. J. Nutr. 110 (5), 790–796. https://doi.org/10.1017/S0007114512006058.

Burneiko, R.C.M., Diniz, Y.S., Galhardi, C.M., Rodrigues, H.G., Ebaid, G.M.X., Faine, L.A., Padovani, C.R., Cicogna, A.C., Novelli, E.L.B., 2006. Interaction of hypercaloric diet and physical exercise on lipid profile, oxidative stress and antioxidant defenses. Food Chem. Toxicol. 44 (7), 1167–1172. https://doi.org/10.1016/j.fct.2006.01.004.

Cahalin, L.P., Myers, J., Kaminsky, L., Briggs, P., Forman, D.E., Patel, M.J., Pinkstaff, S. O., Arena, R., 2014. Current trends in reducing cardiovascular risk factors in the United States: focus on worksite health and wellness. Prog. Cardiovasc. Dis. 56 (5), 476–483. https://doi.org/10.1016/j.pcad.2013.10.002.

Cao, L., Wang, D., Wen, Y., He, H., Chen, A., Hu, D., et al., 2020. Effects of environmental and lifestyle exposures on urinary levels of polycyclic aromatic hydrocarbon metabolites: a cross-sectional study of urban adults in China. Chemosphere 240. https://doi.org/10.1016/j.chemosphere.2019.124898.

Castelli, W.P., 1988. Cholesterol and lipids in the risk of coronary artery disease–the Framingham Heart Study. Can. J. Cardiol. 4 Suppl A, 5A–10A.

Chang, C.C., Chow, C.C., Tellier, L.C., Vattikuti, S., Purcell, S.M., Lee, J.J., 2015. Second-generation PLINK: rising to the challenge of larger and richer datasets. GigaScience 4, 7. https://doi.org/10.1186/s13742-015-0047-8.

Choi, S.W., O'Reilly, P.F., 2019. PRSice-2: Polygenic Risk Score software for biobank-scale data. GigaScience 8. https://doi.org/10.1093/gigascience/giz082.

Cole, C.B., Nikpay, M., McPherson, R., 2015. Gene-environment interaction in dyslipidemia. Curr. Opin. Lipidol. 26, 133–138. https://doi.org/10.1097/MOL.0000000000000160.

Das, S., Forer, L., Schönherr, S., Sidore, C., Locke, A.E., Kwong, A., Vrieze, S.I., Chew, E. Y., Levy, S., McGue, M., Schlessinger, D., Stambolian, D., Loh, P.-R., Iacono, W.G., Swaroop, A., Scott, L.J., Cucca, F., Kronenberg, F., Boehnke, M., Abecasis, G.R., Fuchsberger, C., 2016. Next-generation genotype imputation service and methods. Nat. Genet. 48 (10), 1284–1287. https://doi.org/10.1038/ng.3656.

Do, R., Willer, C.J., Schmidt, E.M., Sengupta, S., Gao, C., Peloso, G.M., et al., 2013. Common variants associated with plasma triglycerides and risk for coronary artery disease. Nat. Genet. 45, 1345–1352. https://doi.org/10.1038/ng.2795.

Dobraca, D., Lum, R., Sjodin, A., Calafat, A.M., Laurent, C.A., Kushi, L.H., et al., 2018. Urinary biomarkers of polycyclic aromatic hydrocarbons in pre- and peri-pubertal girls in Northern California: Predictors of exposure and temporal variability. Environ. Res. 165, 46–54. https://doi.org/10.1016/j.envres.2017.11.011.

Dron, J.S., Hegele, R.A., 2019. The evolution of genetic-based risk scores for lipids and cardiovascular disease. Curr. Opin. Lipidol. 30, 71–81. https://doi.org/10.1097/MOL.0000000000000576.

Ellison, R.C., Zhang, Y., Qureshi, M.M., Knox, S., Arnett, D.K., Province, M.A., et al., 2004. Lifestyle determinants of high-density lipoprotein cholesterol: the National Heart, Lung, and Blood Institute Family Heart Study. Am. Heart J. 147, 529–535. https://doi.org/10.1016/j.ahj.2003.10.033.

Gao, P., da Silva, E., Hou, L., Denslow, N.D., Xiang, P., Ma, L.Q., 2018. Human exposure to polycyclic aromatic hydrocarbons: Metabolomics perspective. Environ. Int. 119, 466–477. https://doi.org/10.1016/j.envint.2018.07.017.

Genomes Project C. Auton, A., Brooks, L.D., Durbin, R.M., Garrison, E.P., Kang, H.M., et al., 2015. A global reference for human genetic variation Nature 526, 68–74. https://doi.org/10.1038/nature15393.

Hannon, B.A., Edwards, C.G., Thompson, S.V., Reeser, G.E., Burd, N.A., Holscher, H.D., et al., 2020. Single Nucleotide polymorphisms related to lipoprotein metabolism are associated with blood lipid changes following regular avocado intake in a randomized control trial among adults with overweight and obesity. J. Nutr. 150, 1379–1387. https://doi.org/10.1093/jn/nxaa054.

Hayashi, G., Cortopassi, G., 2015. Oxidative stress in inherited mitochondrial diseases. Free Radic. Biol. Med. 88, 10–17. https://doi.org/10.1016/j.freeradbiomed.2015.05.039.

Hu, H., Kan, H., Kearney, G.D., Xu, X., 2015. Associations between exposure to polycyclic aromatic hydrocarbons and glucose homeostasis as well as metabolic syndrome in nondiabetic adults. Sci. Total Environ. 505, 56–64. https://doi.org/10.1016/j.scitotenv.2014.09.085.

Hussar, E., Richards, S., Lin, Z.Q., Dixon, R.P., Johnson, K.A., 2012. Human Health Risk Assessment of 16 Priority Polycyclic Aromatic Hydrocarbons in Soils of Chattanooga, Tennessee, USA. Water Air Soil Pollut. 223, 5535–5548. https://doi.org/10.1007/s11270-012-1265-7.

IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2010. Some non-heterocyclic polycyclic aromatic hydrocarbons and some related exposures. IARC Monogr Eval Carcinog Risks Hum. 92, 1-853.

Jin, G., Lv, J., Yang, M., Wang, M., Zhu, M., Wang, T., Yan, C., Yu, C., Ding, Y., Li, G., Ren, C., Ni, J., Zhang, R., Guo, Y.u., Bian, Z., Zheng, Y., Zhang, N., Jiang, Y., Chen, J., Wang, Y., Xu, D., Zheng, H., Yang, L., Chen, Y., Walters, R., Millwood, I.Y., Dai, J., Ma, H., Chen, K., Chen, Z., Hu, Z., Wei, Q., Shen, H., Li, L., 2020. Genetic risk, incident gastric cancer, and healthy lifestyle: a meta-analysis of genome-wide association studies and prospective cohort study. Lancet Oncol. 21 (10), 1378–1386. https://doi.org/10.1016/S1470-2045(20)30460-5.

Jin, Y., Miao, W., Lin, X., Wu, T., Shen, H., Chen, S., Li, Y., Pan, Q., Fu, Z., 2014. Subchronically exposing mice to a polycyclic aromatic hydrocarbon increases lipid accumulation in their livers. Environ. Toxicol. Pharmacol. 38 (2), 353–363. https://doi.org/10.1016/j.etap.2014.07.014.

Kathiresan, S., Willer, C.J., Peloso, G.M., Demissie, S., Musunuru, K., Schadt, E.E., Kaplan, L., Bennett, D., Li, Y., Tanaka, T., Voight, B.F., Bonnycastle, L.L., Jackson, A. U., Crawford, G., Surti, A., Guiducci, C., Burtt, N.P., Parish, S., Clarke, R., Zelenika, D., Kubalanza, K.A., Morken, M.A., Scott, L.J., Stringham, H.M., Galan, P., Swift, A.J., Kuusisto, J., Bergman, R.N., Sundvall, J., Laakso, M., Ferrucci, L., Scheet, P., Sanna, S., Uda, M., Yang, Q., Lunetta, K.L., Dupuis, J., de Bakker, P.I.W., O'Donnell, C.J., Chambers, J.C., Kooner, J.S., Hercberg, S., Meneton, P., Lakatta, E. G., Scuteri, A., Schlessinger, D., Tuomilehto, J., Collins, F.S., Groop, L., Altshuler, D., Collins, R., Lathrop, G.M., Melander, O., Salomaa, V., Peltonen, L., Orho-Melander, M., Ordovas, J.M., Boehnke, M., Abecasis, G.R., Mohlke, K.L., Cupples, L. A., 2009. Common variants at 30 loci contribute to polygenic dyslipidemia. Nat. Genet. 41 (1), 56–65. https://doi.org/10.1038/ng.291.

Kawano, Y., Nishiumi, S., Tanaka, S., Nobutani, K., Miki, A., Yano, Y., Seo, Y., Kutsumi, H., Ashida, H., Azuma, T., Yoshida, M., 2010. Activation of the aryl hydrocarbon receptor induces hepatic steatosis via the upregulation of fatty acid transport. Arch. Biochem. Biophys. 504 (2), 221–227. https://doi.org/10.1016/j.abb.2010.09.001.

Kim, K.H., Jahan, S.A., Kabir, E., Brown, R.J., 2013. A review of airborne polycyclic aromatic hydrocarbons (PAHs) and their human health effects. Environ. Int. 60, 71–80. https://doi.org/10.1016/j.envint.2013.07.019.

Lam, M., Chen, C.-Y., Li, Z., Martin, A.R., Bryois, J., Ma, X., Gaspar, H., Ikeda, M., Benyamin, B., Brown, B.C., Liu, R., Zhou, W., Guan, L., Kamatani, Y., Kim, S.-W., Kubo, M., Kusumawardhani, A.A.A.A., Liu, C.-M., Ma, H., Periyasamy, S., Takahashi, A., Xu, Z., Yu, H., Zhu, F., Chen, W.J., Faraone, S., Glatt, S.J., He, L., Hyman, S.E., Hwu, H.-G., McCarroll, S.A., Neale, B.M., Sklar, P., Wildenauer, D.B., Yu, X., Zhang, D., Mowry, B.J., Lee, J., Holmans, P., Xu, S., Sullivan, P.F., Ripke, S., O'Donovan, M.C., Daly, M.J., Qin, S., Sham, P., Iwata, N., Hong, K.S., Schwab, S.G., Yue, W., Tsuang, M., Liu, J., Ma, X., Kahn, R.S., Shi, Y., Huang, H., 2019. Comparative genetic architectures of schizophrenia in East Asian and European populations. Nat. Genet. 51 (12), 1670–1678. https://doi.org/10.1038/s41588-019-0512-x.

Li, F., Xiang, B., Jin, Y., Li, C., Li, J., Ren, S., Huang, H., Luo, Q., 2019. Dysregulation of lipid metabolism induced by airway exposure to polycyclic aromatic hydrocarbons in C57BL/6 mice. Environ. Pollut. 245, 986–993. https://doi.org/10.1016/j.envpol.2018.11.049.

Li, X., Feng, Y., Deng, H., Zhang, W., Kuang, D., Deng, Q., et al., 2012. The dose-response decrease in heart rate variability: any association with the metabolites of polycyclic aromatic hydrocarbons in coke oven workers? PLoS One 7. https://doi.org/10.1371/journal.pone.0044562.

Licastro, F., Porcellini, E., Caruso, C., Lio, D., Corder, E.H., 2007. Genetic risk profiles for Alzheimer's disease: integration of APOE genotype and variants that up-regulate inflammation. Neurobiol. Aging 28, 1637–1643. https://doi.org/10.1016/j.neurobiolaging.2006.07.007.

Lin, Y., Ramanathan, G., Zhu, Y., Yin, F., Rea, N.D., Lu, X., Tseng, C.-H., Faull, K.F., Yoon, A.J., Jerrett, M., Zhu, T., Qiu, X., Araujo, J.A., 2019. Pro-oxidative and proinflammatory effects after traveling from Los Angeles to Beijing: a biomarker-based natural experiment. Circulation 140 (24), 1995–2004.

Liu, L.-S., Wu, Z., Wang, J., Wang, W., Bao, Y., Cai, J., et al., 2019. 2018 Chinese guidelines for prevention and treatment of hypertension-a report of the revision committee of Chinese guidelines for prevention and treatment of hypertension. 16, 182-245.

Loh, P.-R., Danecek, P., Palamara, P.F., Fuchsberger, C., A Reshef, Y., K Finucane, H., Schoenherr, S., Forer, L., McCarthy, S., Abecasis, G.R., Durbin, R., L Price, A., 2016. Reference-based phasing using the Haplotype Reference Consortium panel. Nat. Genet. 48 (11), 1443–1448. https://doi.org/10.1038/ng.3679.

Lu, X., Huang, J., Mo, Z., He, J., Wang, L., Yang, X., Tan, A., Chen, S., Chen, J., Gu, C.C., Chen, J., Li, Y., Zhao, L., Li, H., Hao, Y., Li, J., Hixson, J.E., Li, Y., Cheng, M., Liu, X., Cao, J., Liu, F., Huang, C., Shen, C., Shen, J., Yu, L., Xu, L., Mu, J., Wu, X., Ji, X.u., Guo, D., Zhou, Z., Yang, Z., Wang, R., Yang, J., Yan, W., Peng, X., Gu, D., 2016. Genetic Susceptibility to Lipid Levels and Lipid Change Over Time and Risk of Incident Hyperlipidemia in Chinese Populations. Circ Cardiovasc Genet. 9 (1), 37–44. https://doi.org/10.1161/CIRCGENETICS.115.001096.

Ma, J., Zhou, Y., Liu, Y., Xiao, L., Cen, X., Li, W., et al., 2019. Association between urinary polycyclic aromatic hydrocarbon metabolites and dyslipidemias in the Chinese general population: A cross-sectional study. Environ. Pollut. 245, 89–97. https://doi.org/10.1016/j.envpol.2018.10.134.

Ma, Y., Harrad, S., 2015. Spatiotemporal analysis and human exposure assessment on polycyclic aromatic hydrocarbons in indoor air, settled house dust, and diet: A review. Environ. Int. 84, 7–16. https://doi.org/10.1016/j.envint.2015.07.006.

Márquez-Luna, C., Loh, P.-R., Price, A.L., 2017. Multiethnic polygenic risk scores improve risk prediction in diverse populations. Genet. Epidemiol. 41 (8), 811–823. https://doi.org/10.1002/gepi.22083.

Martin, A.R., Kanai, M., Kamatani, Y., Okada, Y., Neale, B.M., Daly, M.J., 2019. Clinical use of current polygenic risk scores may exacerbate health disparities. Nat. Genet. 51, 584–591. https://doi.org/10.1038/s41588-019-0379-x.

Mbikay, M., Mayne, J., Chretien, M., 2020. The enigma of soluble LDLR: could inflammation be the key? Lipids Health Dis. 19, 17. https://doi.org/10.1186/s12944-020-1199-9.

Miao, L., Yin, R.-X., Hu, X.-J., Wu, D.-F., Cao, X.-L., Li, Q., Yan, T.-T., Aung, L.H.H., Wu, J.-Z., Lin, W.-X., 2012. Association of rs2072183 SNP and serum lipid levels in the Mulao and Han populations. Lipids Health Dis. 11 (1) https://doi.org/10.1186/1476-511X-11-61.

Miyake, J.H., Wang, S.L., Davis, R.A., 2000. Bile acid induction of cytokine expression by macrophages correlates with repression of hepatic cholesterol 7alpha-hydroxylase. J. Biol. Chem. 275, 21805–21808. https://doi.org/10.1074/jbc.C000275200.

Murray, A., Cluett, C., Bandinelli, S., Corsi, A.M., Ferrucci, L., Guralnik, J., et al., 2009. Common lipid-altering gene variants are associated with therapeutic intervention thresholds of lipid levels in older people. Eur. Heart J. 30, 1711–1719. https://doi.org/10.1093/eurheartj/ehp161.

Namboodiri, K.K., Kaplan, E.B., Heuch, I., Elston, R.C., Green, P.P., Rao, D.C., Laskarzewski, P., Glueck, C.J., Rifkind, B.M., Skolnick, M.H., 1985. The Collaborative Lipid Research Clinics Family Study: biological and cultural determinants of familial resemblance for plasma lipids and lipoproteins. Genet. Epidemiol. 2 (3), 227–254.

Nie, X., Mu, G., Yang, S., Ye, Z., Wang, M., Wang, D., et al., 2021. The methylation of the AMER3 gene mediates the negative association between urinary polycyclic aromatic hydrocarbon metabolites and fasting plasma glucose in non-smokers: A new clue for the development of hypoglycemic agents. J. Hazard Mater. 419 https://doi.org/10.1016/j.jhazmat.2021.126548.

Patel, A.P., Mehta, S.S., White, A.J., Niehoff, N.M., Arroyave, W.D., Wang, A., et al., 2021. Urinary polycyclic aromatic hydrocarbon metabolites and mortality in the United States: A prospective analysis. PLoS One 16. https://doi.org/10.1371/journal.pone.0252719.

Peloso, G.M., Auer, P.L., Bis, J.C., Voorman, A., Morrison, A.C., Stitziel, N.O., et al., 2014. Association of low-frequency and rare coding-sequence variants with blood lipids and coronary heart disease in 56,000 whites and blacks. Am. J. Hum. Genet. 94, 223–232. https://doi.org/10.1016/j.ajhg.2014.01.009.

Penning, T.M., Ohnishi, S.T., Ohnishi, T., Harvey, R.G., 1996. Generation of reactive oxygen species during the enzymatic oxidation of polycyclic aromatic hydrocarbon trans-dihydrodiols catalyzed by dihydrodiol dehydrogenase. Chem. Res. Toxicol. 9, 84–92. https://doi.org/10.1021/tx950055s.

Ramesh, A., Hood, D.B., Inyang, F., Greenwood, M., Nyanda, A.M., Archibong, A.E., et al., 2002. Comparative metabolism, bioavailability, and toxicokinetics of benzo [a] pyrene in rats after acute oral, inhalation, and intravenous administration. 22, 969-980.

Ranjbar, M., Rotondi, M.A., Ardern, C.I., Kuk, J.L., 2015. Urinary biomarkers of polycyclic aromatic hydrocarbons are associated with cardiometabolic health risk. PLoS One 10. https://doi.org/10.1371/journal.pone.0137536.

Reiner, Z., 2017. Hypertriglyceridaemia and risk of coronary artery disease. Nat. Rev. Cardiol. 14, 401–411. https://doi.org/10.1038/nrcardio.2017.31.

Riley, R.D., Ensor, J., Snell, K.I.E., Harrell Jr., F.E., Martin, G.P., Reitsma, J.B., et al., 2020. Calculating the sample size required for developing a clinical prediction model. BMJ 368, m441. https://doi.org/10.1136/bmj.m441.

Song, Y., Hou, J., Huang, X., Zhang, X., Tan, A., Rong, Y.i., Sun, H., Zhou, Y., Cui, X., Yang, Y., Guo, Y., Zhang, Z., Luo, X., Zhang, B., Hou, F., He, X., Xie, J., Wu, T., Chen, W., Yuan, J., 2014. The Wuhan-Zhuhai (WHZH) cohort study of environmental air particulate matter and the pathogenesis of cardiopulmonary diseases: study design, methods and baseline characteristics of the cohort. BMC Public Health. 14 (1) https://doi.org/10.1186/1471-2458-14-994.

Spracklen, C.N., Chen, P., Kim, Y.J., Wang, X., Cai, H., Li, S., et al., 2017. Association analyses of East Asian individuals and trans-ancestry analyses with European individuals reveal new loci associated with cholesterol and triglyceride levels. Hum. Mol. Genet. 26, 1770–1784. https://doi.org/10.1093/hmg/ddx062.

Tang, Z.-H., Li, T.-H., Peng, J., Zheng, J., Li, T.-T., Liu, L.-S., Jiang, Z.-S., Zheng, X.-L., 2019. PCSK9: A novel inflammation modulator in atherosclerosis? J. Cell. Physiol. 234 (3), 2345–2355. https://doi.org/10.1002/jcp.27254.

Teslovich, T.M., Musunuru, K., Smith, A.V., Edmondson, A.C., Stylianou, I.M., Koseki, M., et al., 2010. Biological, clinical and population relevance of 95 loci for blood lipids. Nature 466, 707–713. https://doi.org/10.1038/nature09270.

Thai, P.K., Heffernan, A.L., Toms, L.-M., Li, Z., Calafat, A.M., Hobson, P., Broomhall, S., Mueller, J.F., 2016. Monitoring exposure to polycyclic aromatic hydrocarbons in an Australian population using pooled urine samples. Environ. Int. 88, 30–35.

Tikkanen, E., Tuovinen, T., Widén, E., Lehtimäki, T., Viikari, J., Kähönen, M., Peltonen, L., Raitakari, O.T., Ripatti, S., 2011. Association of known loci with lipid levels among children and prediction of dyslipidemia in adults. Circ. Cardiovasc. Genet. 4 (6), 673–680.

Varga, T.V., Sonestedt, E., Shungin, D., Koivula, R.W., Hallmans, G., Escher, S.A., et al., 2014. Genetic determinants of long-term changes in blood lipid concentrations: 10-year follow-up of the GLACIER study. PLoS Genet. 10 https://doi.org/10.1371/journal.pgen.1004388.

Vogel, C.F.A., Van Winkle, L.S., Esser, C., Haarmann-Stemmann, T., 2020. The aryl hydrocarbon receptor as a target of environmental stressors - Implications for pollution mediated stress and inflammatory responses. Redox Biol. 34, 101530 https://doi.org/10.1016/j.redox.2020.101530.

Willer, C.J., Schmidt, E.M., Sengupta, S., Peloso, G.M., Gustafsson, S., Kanoni, S., et al., 2013. Discovery and refinement of loci associated with lipid levels. Nat. Genet. 45, 1274–1283. https://doi.org/10.1038/ng.2797.

Xi, Y., Niu, L., Cao, N., Bao, H., Xu, X., Zhu, H., et al., 2020. Prevalence of dyslipidemia and associated risk factors among adults aged >=35 years in northern China: a cross-sectional study. BMC Public Health 20, 1068. https://doi.org/10.1186/s12889-020-09172-9.

Yang, B.-Y., Bloom, M.S., Markevych, I., Qian, Z.(., Vaughn, M.G., Cummings-Vaughn, L. A., Li, S., Chen, G., Bowatte, G., Perret, J.L., Dharmage, S.C., Heinrich, J., Yim, S.-L., Lin, S., Tian, L., Yang, M.o., Liu, K.-K., Zeng, X.-W., Hu, L.-W., Guo, Y., Dong, G.-H., 2018. Exposure to ambient air pollution and blood lipids in adults: The 33 Communities Chinese Health Study. Environ. Int. 119, 485–492. https://doi.org/10.1016/j.envint.2018.07.016.

Yang, P., Wang, Y.-X., Sun, L.i., Chen, Y.-J., Liu, C., Huang, L.-L., Lu, W.-Q., Zeng, Q., 2017. Urinary metabolites of polycyclic aromatic hydrocarbons, sperm DNA damage and spermatozoa apoptosis. J. Hazard. Mater. 329, 241–248.

Yu, Y.i., Wyszynski, D.F., Waterworth, D.M., Wilton, S.D., Barter, P.J., Kesäniemi, Y.A., Mahley, R.W., McPherson, R., Waeber, G., Bersot, T.P., Ma, Q., Sharma, S.S., Montgomery, D.S., Middleton, L.T., Sundseth, S.S., Mooser, V., Grundy, S.M., Farrer, L.A., 2005. Multiple QTLs influencing triglyceride and HDL and total cholesterol levels identified in families with atherogenic dyslipidemia. J. Lipid Res. 46 (10), 2202–2213.

Zhou, Y., Sun, H., Xie, J., Song, Y., Liu, Y., Huang, X., Zhou, T., Rong, Y.i., Wu, T., Yuan, J., Chen, W., 2016. Urinary Polycyclic Aromatic Hydrocarbon Metabolites and Altered Lung Function in Wuhan, China. Am. J. Respir. Crit. Care Med. 193 (8), 835–846.