



Metabolic alterations bridge exposure to urinary halogenated phenols and bisphenols to dyslipidemia: Evidence from an e-waste recycling area

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ABSTRACT

Halogenated phenols and bisphenols are metabolic-disrupting chemicals related to electronic waste (e-waste) dismantling activities. However, their adverse effects on lipid metabolism and the underlying mechanisms remain insufficiently understood. Based on a cross-sectional study of 227 e-waste workers and residents from an e-waste recycling area in China, we measured 11 urinary halogenated phenols and bisphenols, quantified four serum lipid parameters, and performed untargeted serum metabolomics. Dyslipidemia and its subtypes (hypercholesterolemia, hypertriglyceridemia, and hyper low-density lipoprotein cholesterol) were defined according to clinical criteria. After covariate adjustment, six phenolic compounds (PCs) and their mixture were associated with increased odds of dyslipidemia and its subtypes, with 3,5-dichlorophenol contributing most to dyslipidemia, hyper low-density lipoprotein cholesterol, and hypertriglyceridemia, whereas 3,4-dichlorophenol contributed most to hypercholesterolemia. Stronger associations were observed in males, normal-weight individuals, and those aged <60 years. Mediation analysis identified nine metabolites that significantly mediated these associations (proportions mediated: 14.8%–63.7%), annotated to amino acid, energy, and retinol metabolism pathways. Hierarchical partitioning revealed that PC exposure alone explained 4.28% of the variance in lipid metabolism, indicating a meaningful contribution. These findings provide potential mechanistic insights into the associations of halogenated phenol and bisphenol exposure with lipid homeostasis and highlight the need to reduce exposure to these chemicals among e-waste workers and nearby residents.

1. Introduction

Electronic waste (e-waste) has become one of the fastest-growing solid waste streams worldwide (Kuang et al., 2026). According to the Global E-waste Monitor (2024), global e-waste generation reached a record 62 million metric tons in 2022, representing an 82% increase since 2010, yet only 22.3% was documented as formally collected and recycled (ITU, 2024). A substantial proportion of e-waste, including discarded circuit boards, wires, plastics, and metals, is dumped, traded, or processed under environmentally unsound conditions, resulting in the release of complex mixtures of toxic substances into the surrounding

environment (Kuang et al., 2026). More than 1000 hazardous substances have been identified as either components of e-waste or products of unsound recycling activities, such as metals, polycyclic aromatic hydrocarbons, and phenolic compounds (PCs) (ITU, 2024).

Among these contaminants, halogenated phenols (HPs), bisphenols (BPs), and their precursors have attracted increasing attention because of their potential to disrupt metabolic homeostasis (Khani et al., 2023; Lin et al., 2025; Michałowicz et al., 2022; Tang et al., 2025). BPs are widely used in bisphenol-based materials (Liao and Kannan, 2013), including polycarbonate plastics and epoxy resins, and may be released from these materials during mechanical abrasion, shredding, and

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thermal degradation associated with e-waste dismantling and treatment (Liu et al., 2011; Xie et al., 2026). Brominated phenols may be used directly as additives or formed through the environmental degradation or in vivo biotransformation of brominated flame retardants (Ho et al., 2012; Koch and Sures, 2018; Michałowicz et al., 2022). Chlorinated phenols in the environment are primarily associated with the use of industrial chemicals (Olaniran and Igbinsola, 2011). In the context of e-waste recycling, however, chlorinated phenols can be generated via halogen exchange reactions between brominated flame retardants and chlorine-containing polymers (Zhang et al., 2024a), as well as through de novo synthesis from carbonaceous residues and inorganic chlorine sources (Peng et al., 2016). In addition to these environmental formation pathways, chlorinated phenols may be formed in the human body through the metabolism of other chlorinated organic compounds, such as chlorobenzenes and hexachlorocyclohexane (Angerer et al., 1983; Bogaards et al., 1995). Recent biomonitoring studies have reported significantly higher urinary concentrations of several HPs and BPs among residents of e-waste recycling areas than among reference populations (Kuang et al., 2026; Lin et al., 2020). Notably, a panel comprising 2,4,6-tribromophenol (2,4,6-Tri-BP), 4-bromophenol (4-Mono-BP), and 2,4,5-trichlorophenol (2,4,5-Tri-CP) showed strong discriminatory power between exposed and non-exposed groups (Kuang et al., 2026). Although 4-mono-BP has not commonly been reported as a predominant bromophenol in e-waste environments or a major polybrominated diphenyl ether metabolite (Lin et al., 2020), its contribution to exposure classification supports its inclusion as a complementary indicator of e-waste-related exposure. Furthermore, urinary chlorophenol biomarkers capture signals from diverse exposure sources, thus contributing to a more comprehensive reflection of e-waste exposure profiles (Angerer et al., 1983; Peng et al., 2016). Among these, 2,4,5-Tri-CP was also identified as a top-ranked feature in a machine-learning prediction model, supporting the representativeness of these chlorophenol biomarkers. Nevertheless, current studies have mainly focused on exposure characterization, and the health implications of elevated exposure to HP, BP, or their precursors in e-waste recycling areas remain insufficiently understood.

Dyslipidemia is a major modifiable risk factor for cardiovascular disease, which remains the leading cause of death and disability worldwide (Eckhardt and Kaiflie, 2024; Murray et al., 2020; Parvez et al., 2021). Conventional contributors, including unhealthy diet, physical inactivity, and genetic susceptibility, account for only part of the variation in dyslipidemia risk, suggesting a potential contribution from environmental exposures (Zheng et al., 2026). Epidemiological evidence linking phenols to lipid disorders is emerging. Short-term exposure to BPs and triclosan (TCS) has been associated with unfavorable changes in blood lipid profiles (Xiang et al., 2024), and 2,5-dichlorophenol (2,5-Di-CP) has been linked to reduced high-density lipoprotein cholesterol (HDL-C) and impaired lipid metabolism (Wei and Zhu, 2016). Experimental studies further suggest that HPs, BPs, and related precursors can disturb lipid homeostasis by impairing fatty acid oxidation, enhancing lipid synthesis, promoting lipid droplet accumulation, and inducing oxidative stress (Lin et al., 2025; Sun et al., 2020; Sun et al., 2026). Despite these documented links, two critical gaps remain to be addressed. First, most evidence comes from general populations with relatively low exposure levels, and it is unclear whether these associations persist under the higher exposure levels and more complex pollutant mixtures typical of e-waste recycling areas (Hu et al., 2026). Second, mechanistic studies have largely focused on selected pathways, such as oxidative stress and nuclear receptor signaling, leaving the global metabolic perturbations associated with HP and BP exposure largely unexplored (Murray et al., 2020; Roth et al., 2020).

To address these gaps, we analyzed matched urine and serum samples from 227 participants living in an e-waste recycling area in China. Urinary concentrations of 11 PCs were quantified as biomarkers of internal HP and BP exposure. Serum lipid indicators were measured, and dyslipidemia and its subtypes were defined according to standardized

clinical criteria. We examined associations of urinary PCs with dyslipidemia and its subtypes after covariate adjustment. Untargeted serum metabolomics was then used to characterize global metabolic perturbations and to identify metabolites linking phenolic exposure to dyslipidemia. Hierarchical partitioning analysis was further applied to estimate the relative contribution of phenolic exposure to lipid metabolism variance in comparison with other covariates. This study aimed to clarify the associations between urinary HP and BP exposure and dyslipidemia, identify key metabolic alterations, and provide evidence for priority pollutants and potential toxic targets under the high-exposure and co-exposure scenarios typical of e-waste recycling areas.

2. Materials and methods

2.1. Study population

From April to September 2020, volunteers were recruited from Longtang town, Qingyuan City, Guangdong Province, a typical e-waste recycling area in southeastern China. Eligible participants were adults aged ≥ 18 years who had resided locally for an extended period. Exclusion criteria included malignant tumors, pregnancy or lactation. From the initial recruitment population, we further excluded individuals with: (1) self-reported history of cardiovascular diseases, liver or kidney dysfunction; (2) diabetes, hypertension, or other chronic diseases requiring long-term medication; (3) use of lipid-lowering medications within the past month; (4) missing basic information or unavailability of paired urine and blood samples. A total of 227 participants were enrolled, including 154 individuals with dyslipidemia and 73 healthy controls. Dyslipidemia was defined according to the Chinese Guidelines for the Prevention and Treatment of Dyslipidemia in Adults based on fasting lipid profiles: total cholesterol ≥ 6.2 mmol/L, low-density lipoprotein cholesterol ≥ 4.1 mmol/L, triglyceride ≥ 2.3 mmol/L, or high-density lipoprotein cholesterol < 1.0 mmol/L (Li, 2023). Dyslipidemia was further categorized into four subtypes: hypercholesterolemia (hyperTC), hyper low-density lipoprotein cholesterol (hyperLDL-C), hypertriglyceridemia (hyperTG), and hypoHDL-C. Paired blood and urine samples were collected from each participant, quickly transported to the laboratory on dry ice, and then stored at -80°C for later analysis. All participants provided written informed consent, and this protocol was reviewed and formally approved by the Research Ethics Committee of South China Normal University, approval number [SCNU-SLS-2016-001].

2.2. Quantification of urinary PCs

Eleven phenolic compounds were selected for quantitative analysis based on their high detection frequencies ($>80\%$) in the urine of populations residing in e-waste recycling areas, as determined in our previous large-scale biomonitoring study profiling over 200 urinary organic pollutants among 2028 participants from e-waste recycling sites and reference industrial parks (Kuang et al., 2026). These compounds included 4-chlorophenol (4-Mono-CP), 2,5-Di-CP, 3,4-dichlorophenol (3,4-Di-CP), 3,5-dichlorophenol (3,5-Di-CP), 2,4,5-Tri-CP, 2,3,4,6-tetrachlorophenol (2,3,4,6-Tetra-CP), 4-chlorocatechol (4-CCT), 4-Mono-BP, 2,4,6-Tri-BP, bisphenol S (BPS), and TCS. Urinary PCs were quantified using liquid chromatography–high-resolution mass spectrometry (LC-HRMS; Q Exactive Orbitrap, Thermo Fisher Scientific, USA). Detailed procedures for chemicals, sample preparation, instrumental parameters, and quality control (QC) measures are provided in Text S1 and Table S1. The limits of detection (LOD) ranged from 0.001 to 0.116 $\mu\text{g/mL}$, and the spiking recoveries were 91.8–116% (Table S2). Relative standard deviations (RSDs) were $<15\%$ for all analytes except 2,5-Di-CP (19.0%). Urinary creatinine was measured using a commercial kit (Cayman Chemical, Ann Arbor, MI, USA) to adjust for dilution. Representative chromatograms are shown in Fig. S1.

2.3. Serum metabolomics profiling

We performed untargeted metabolomic profiling on fasting peripheral venous blood samples using ultra-high performance liquid chromatography coupled with Orbitrap mass spectrometry (UHPLC-Orbitrap MS; Q Exactive, Thermo Fisher Scientific, USA) fitted with a heated electrospray ionization source. Comprehensive details on sample pretreatment, chromatographic conditions, mass spectrometry settings, and quality control are available in Text S2. Raw data were processed using Compound Discoverer software (version 3.3, Thermo Fisher Scientific, Waltham, MA). Peak extraction was performed with a mass tolerance of 10 ppm, requiring a signal-to-noise ratio ≥ 5 . Only compounds detected in at least 50% of samples were retained. Batch effect correction was carried out using a random forest-based algorithm, and peak area normalization was performed using the constant median algorithm. Metabolites were identified and annotated by matching mass spectral data with reference databases (mass accuracy < 5 ppm). The reliability of the metabolomics data was evaluated by principal component analysis, which showed tight clustering of QC samples compared to test samples in both negative (Fig. S2) and positive (Fig. S3) ion modes, indicating excellent system stability throughout the analysis. After excluding features with poor reproducibility (RSDs $> 30\%$ in QC samples), a total of 507 metabolites were retained for subsequent analysis. All metabolites were detected in more than 80% of samples.

2.4. Potential covariates

Covariates were selected based on their potential associations with PC exposure or lipid outcomes as reported in previous literature (Lin et al., 2020; Murray et al., 2020). To avoid selection bias and inflated type I error rates that may arise from outcome-driven variable selection, we performed hierarchical partitioning analysis to assess the contribution of each covariate to PC exposure variability, as confounders must be associated with the exposure. This approach quantifies the independent contribution of each covariate to PC exposure levels while accounting for multicollinearity. Using this approach, the nine selected covariates collectively explained 9.14%–10.24% of the variance in individual phenolic compounds, with each covariate contributing similarly and no single variable dominating the explained variance (Fig. S4). Therefore, all nine covariates were retained in subsequent multivariable models to minimize potential confounding. The included covariates were: age, body mass index (BMI), gender, education level, annual income level, occupation, smoking status, drinking status, and daily exercise duration.

2.5. Statistical method

We summarized the demographic characteristics and PC exposure distributions of the study population using descriptive analyses. Values below the limit of detection (LOD) were substituted with $\text{LOD}/\sqrt{2}$. Because the phenolic compound concentrations were skewed, we applied $\log_{10}$ transformation to normalize the data, followed by standardization before statistical modeling. Missing covariate data were addressed by multiple imputation with chained equations, producing five imputed datasets (mean missing rate $< 5\%$), which were subsequently pooled using Rubin's rules (Hayati Rezvan et al., 2015). Spearman's rank correlation was used to assess associations between individual PCs.

To evaluate the associations of individual PCs with dyslipidemia and its subtypes, we applied multivariable logistic regression models to calculate the odds ratios (ORs) and 95% confidence intervals (CIs). All models were adjusted for predetermined covariates. PCs concentrations were examined using two complementary approaches to ensure robustness and to capture the shape of the dose-response relationship: (1) as continuous variables, providing an overall estimate of effect per unit increase; and (2) as categorical variables based on tertiles (with the lowest tertile as the reference), allowing for the assessment of nonlinear

associations. Building on these single-pollutant analyses, we further performed weighted quantile sum (WQS) regression to evaluate the overall mixture effect of PCs and identify the most influential contributors. The direction of the mixture effect was prespecified based on the associations observed in the single-pollutant models. Concentrations of individual PCs were categorized into quartiles, and the WQS index was constructed using 1000 bootstrap iterations to estimate the mixture effect in the designated direction, with the same sets of covariates adjusted in all models. The resulting weights, which sum to 1 and range from 0 to 1, reflect the relative contribution of each PC to the overall mixture effect. Additionally, to assess the robustness of the findings and explore potential effect modification, stratified analyses were subsequently conducted by age, gender, and BMI, which were selected based on their well-recognized roles as effect modifiers in the associations between environmental exposures and metabolic disorders. In each stratum, logistic regression models were fitted with the same covariates as in the primary analysis, excluding the stratification variable.

For metabolomics analyses, a comprehensive workflow was implemented, comprising a metabolome-wide association study (MWAS), a meet-in-the-middle (MITM) approach, pathway enrichment analysis, and mediation effect analysis. MWAS was performed to capture metabolic features associated with exposures and outcomes. Linear regression models were used to identify metabolites associated with individual PC concentrations, while logistic regression models were used to screen metabolites associated with dyslipidemia and its subtypes. All models were adjusted for covariates. The MITM approach was subsequently applied to select overlapping metabolites that showed significant associations with both the exposure and the outcomes. Pathway enrichment analysis of these overlapping metabolites was conducted using MetaboAnalyst 6.0 with the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway database for *Homo sapiens* to explore their biological relevance and to prioritize functionally meaningful metabolites for further investigation. Based on the enrichment results, simple mediation analysis was conducted to evaluate the potential mediating roles of overlapping metabolites that mapped to significantly enriched pathways. For each candidate mediator, the overall effect, average causal mediation effect, average direct effect, and the proportion mediated were estimated using 1000 bootstrap iterations, with all models adjusted for the same covariates as in the MWAS. The Mann-Whitney *U* test was used to compare the relative abundances of mediator metabolites between dyslipidemia cases and healthy controls. To visualize the interrelationships among enriched pathways and the distribution of mediator metabolites, we constructed a metabolic network based on all significantly enriched KEGG pathways and mapped the selected mediator metabolites onto this network to examine their distribution and identify potential metabolic interconnections.

Hierarchical partitioning analysis was used to quantify the contributions of individual PCs, epidemiological factors, and their interactions to dyslipidemia and its subtypes. This method addresses multicollinearity by averaging each variable's independent contribution across all subset models, decomposing the total explained variance (R^2) into independent contributions. Using the "rdacca.hp" package, a multivariate logistic regression model was first fitted to the four lipid outcomes treated as a matrix of dependent variables, allowing the simultaneous decomposition of explained variance across all outcomes. Subsequently, separate logistic regression models were fitted for each individual outcome to enable detailed assessment of disease-specific contribution patterns. For both the overall and individual models, the total explained variance was partitioned into contributions from individual PCs, epidemiological factors, and interaction terms among these variables. The relative importance of each predictor was expressed as its independent contribution to the model R^2 , providing a direct quantitative comparison of explanatory power across risk factor categories.

All statistical analyses were performed using R software (version 4.1.1, R Foundation for Statistical Computing, Vienna, Austria). Two-sided *p*-values < 0.05 were considered statistically significant.

3. Results

3.1. General characteristics and PC exposure levels in the study population

Demographic and clinical characteristics of the study population are summarized in Table S3. A total of 227 participants were included, with a mean age of 55.9 years. The majority of participants were male (70.9%), and 63.9% were engaged in the e-waste recycling industry. The overall prevalence of dyslipidemia was 67.8%, with hyperLDL-C (54.2%) and hyperTC (43.6%) being the most prevalent subtypes. Urinary concentrations of 11 PCs are presented in Fig. S5 and Table S4. All analytes were detected in at least 74% of urine samples, with 3,5-Di-CP, 4-Mono-CP, and BPS detected in 100% of samples. The highest geometric mean concentration was observed for 4-Mono-CP (31.4 $\mu\text{g/g}$ creatinine), followed by TCS (6.40 $\mu\text{g/g}$), BPS (5.11 $\mu\text{g/g}$), and 4-CCT (4.69 $\mu\text{g/g}$). Concentration distributions were markedly right-skewed, with substantial inter-individual variability spanning several orders of magnitude (e.g., BPS ranged from 0.120 to 163 $\mu\text{g/g}$), indicating widespread but heterogeneous exposure patterns.

3.2. Associations of individual PCs with dyslipidemia and its subtypes

Four lipid metabolism diseases, including dyslipidemia, hyperLDL-C, hyperTC, and hyperTG, were selected for analysis based on adequate

sample sizes to ensure robust association estimates. In single-pollutant models, several PCs were positively associated with the risk of these outcomes. When modeled as continuous variables, both 3,5-Di-CP and 3,4-Di-CP were significantly associated with elevated risks of hyperLDL-C and hyperTC (Fig. S6). To further evaluate dose-response relationships, exposures were categorized into tertiles (Fig. 1). Compared with the lowest tertile, the highest tertile of 4-Mono-CP, 3,5-Di-CP, 3,4-Di-CP, 2,4,5-Tri-CP, 2,3,4,6-Tetra-CP, and TCS was associated with increased risk of dyslipidemia ($p < 0.05$). Additionally, the second tertile of 3,4-Di-CP also showed a positive association with dyslipidemia. For specific dyslipidemia subtypes, exposure to 3,5-Di-CP and 3,4-Di-CP at the highest tertile was significantly linked to increased hyperLDL-C risk, with the second tertile of 3,4-Di-CP also showing a positive association. Regarding hyperTC, both the second and highest tertiles of 3,4-Di-CP conferred elevated risk ($p < 0.05$). Moreover, the highest tertiles of 4-Mono-CP and 3,5-Di-CP were positively associated with increased risk of hyperTG ($p < 0.05$). Detailed ORs and 95% CIs for both continuous and categorical analyses are presented in Table S5 and Table S6.

3.3. Effect modification by age, BMI, and gender

We further examined whether the associations between PC exposure and dyslipidemia and its subtypes varied across age, BMI, and gender strata. Age was categorized into two groups: 18–60 years (young and middle-aged) and 60–90 years (elderly). Compared with the elderly

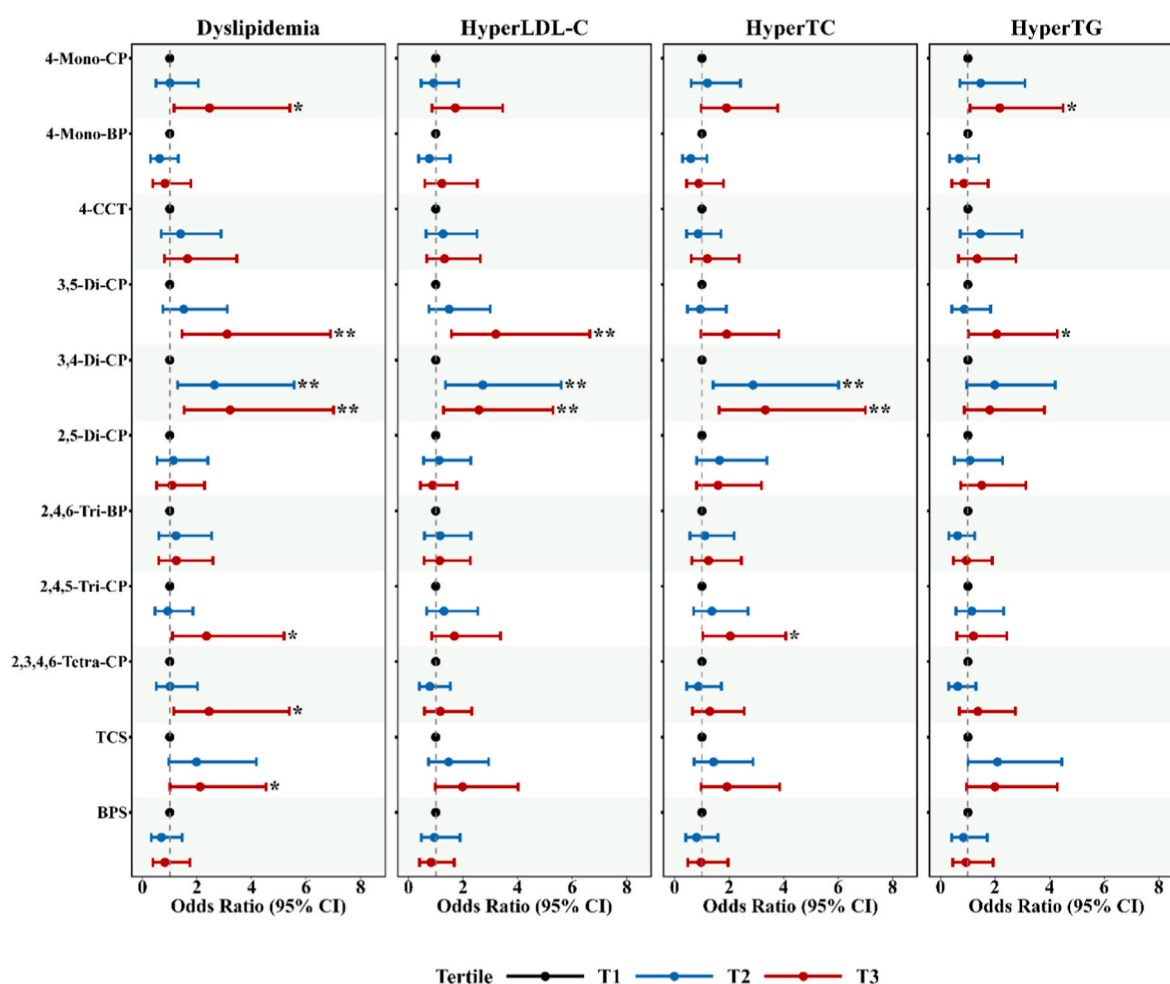


Fig. 1. Associations of individual PC exposures with dyslipidemia and its subtypes based on tertile analyses. The lowest tertile (T1) served as the reference, with an OR of 1.00 (black dot). Blue and red dots represent ORs for the middle tertile (T2) and the highest tertile (T3), respectively. The dashed vertical line indicates the null association (OR = 1.00). Asterisks denote statistical significance: * $p < 0.05$, ** $p < 0.01$. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

group, the young and middle-aged group exhibited a higher risk of dyslipidemia, hyperLDL-C, and hyperTC, primarily associated with exposure to 3,5-Di-CP and 3,4-Di-CP (Fig. S7). Conversely, these same exposures were associated with a stronger risk of hyperTG in the elderly group. When stratified by BMI status, participants with normal weight (BMI of 18.5–23.9 kg/m²) showed a higher risk of dyslipidemia and hyperTC associated with exposure to specific PCs, particularly 3,5-Di-CP, 3,4-Di-CP, TCS, and 2,4,5-Tri-CP, compared with those who were overweight or obese (BMI of ≥ 24 kg/m²). Given that many disease risk factors are gender-specific, we also examined gender differences in the associations between PC exposure and disease risk. Significant positive associations of 3,5-Di-CP and 3,4-Di-CP with dyslipidemia and hyperTC were observed only in males, suggesting that males may be more susceptible to the adverse lipid effects of these specific PCs.

3.4. Associations of PC mixtures with dyslipidemia and its subtypes

Given the moderate inter-correlations among individual PCs (Fig. S8), we employed WQS regression to assess the joint effect of the PC mixture. Results indicated that exposure to the PC mixture was significantly associated with elevated risks of dyslipidemia and its subtypes

(Fig. 2). Each quartile increases in the WQS index corresponded to 309% higher odds of dyslipidemia (95% CI: 1.72–9.74), with 3,5-Di-CP contributing most to the mixture effect (31.8%), followed by TCS (28.8%), 4-Mono-CP (20.7%), 3,4-Di-CP (10.4%), 2,3,4,6-Tetra-CP (0.044%), and 2,4,5-Tri-CP (0.039%). For hyperLDL-C, the odds increased by 121% per quartile increment in the WQS index (95% CI: 1.12–4.37), with 3,4-Di-CP (56.4%) as the predominant chemical, followed by TCS (24.5%). Regarding hyperTG, each quartile increases in the WQS index corresponded to 124% higher odds (95% CI: 1.19–4.22), with 3,5-Di-CP (41.0%), 4-Mono-CP (22.9%), 3,4-Di-CP (22.0%), and TCS (13.6%) as the main contributors.

3.5. Metabolites associated with PC exposure and dyslipidemia outcomes

Based on the mixture model results, five PCs (i.e., 3,5-Di-CP, 3,4-Di-CP, TCS, 4-Mono-CP, and 2,4,5-Tri-CP) were selected for metabolomics analysis due to their substantial contributions to the mixture effects. After covariate adjustment, these five PCs were significantly associated with changes in 507 detected serum metabolites. Specifically, 3,5-Di-CP

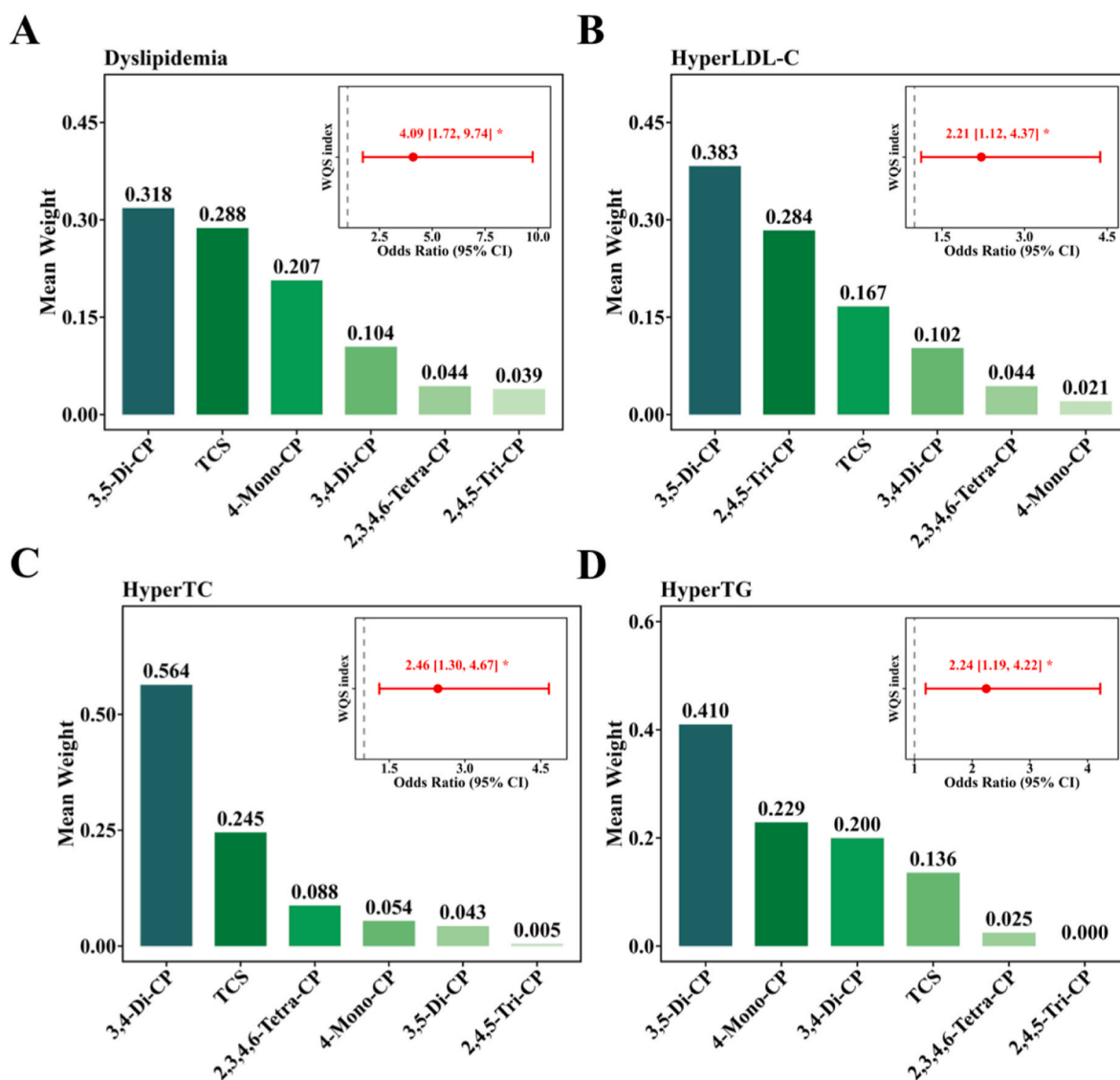


Fig. 2. Associations of the PC mixture with dyslipidemia and its subtypes based on WQS regression. Four panels are presented for dyslipidemia (A), hyperLDL-C (B), hyperTC (C), and hyperTG (D). In each panel, the main plot displays the individual PC weights from the WQS model, with the inset showing the overall mixture effect. The dashed vertical line indicates the null association (OR = 1.00). Asterisks denote statistical significance: * $p < 0.05$.

was associated with 97 metabolites, followed by 3,4-Di-CP (282 metabolites), TCS (108 metabolites), 4-Mono-CP (55 metabolites), and 2,4,5-Tri-CP (217 metabolites) (Fig. 3 and S9). Higher exposure levels of these PCs were primarily linked to downregulation of lipids, including cholesteryl sulfate, myristyl sulfate, 16-nitroxystearate, lecithin, LysoPC (20:4), and trans-2-hexadecenoyl-L-carnitine, as well as upregulation of docosahexaenoic acid. In parallel, the MWAS identified serum metabolites significantly associated with dyslipidemia and its subtypes. A total of 89 metabolites were associated with dyslipidemia, 132 with hyperLDL-C, 171 with hyperTC, and 14 with hyperTG. Notably, higher levels of shikimic acid, DL-tryptophan, and ethylenediaminetetraacetic acid were associated with a reduced risk of both dyslipidemia and its subtypes.

Using the MITM approach, we examined the overlap between metabolites associated with the five PCs and those linked to dyslipidemia or its subtypes (overlapping metabolite names are provided in Table S7). A total of 88 overlapping metabolites were identified between the PCs and dyslipidemia, predominantly lipids, amino acids and their derivatives, and organic acids (Fig. 3 and S9). For hyperTG, 14 overlapping metabolites were found, the majority of which were amino acids and their derivatives. Additionally, 131 and 169 overlapping metabolites were identified between the PCs and hyperLDL-C and hyperTC, respectively, with a similar compositional pattern dominated by these three metabolite classes.

3.6. Pathway enrichment and mediation analyses

To explore the biological relevance of the identified overlapping metabolites, pathway enrichment analysis was performed using the KEGG database. A total of nine distinct metabolic pathways were

significantly enriched across the four MITM outcomes, including arginine biosynthesis, alanine/aspartate/glutamate metabolism, arginine/proline metabolism, glycine/serine/threonine metabolism, butanoate metabolism, retinol metabolism, the citric acid cycle, glyoxylate/dicarboxylate metabolism, and fatty acid biosynthesis (Fig. S10). From these enriched pathways, overlapping metabolites were further evaluated for mediation effects. Nine metabolites exhibited significant mediation effects, with mediation proportions ranging from 14.8% to 63.7% (Fig. 4). The strongest mediation effect was observed for 4-hydroxy-2-oxoglutarate, which accounted for 63.7% of the association between 3,4-Di-CP and hyperTC. Only one metabolite, N-acetyl-L-glutamate, was found to mediate the association between PC exposure and dyslipidemia, explaining 14.8% of the total effect. For hypertriglyceridemia, similarly, the sole mediator was myristic acid, with a mediated proportion ranging from 20.5% to 31.8%. Of note, N-acetyl-L-glutamate and creatine mediated a substantial portion (ranging from 18.2% to 43.5%) of the associations of PC exposure with hyperTC and hyperLDL-C, implicating them as potential critical biological hubs underlying these adverse outcomes. Additionally, several metabolites, including retinoate, retinal, 2-oxoglutarate, 4-aminobutanoate, and pyruvate, served as significant mediators for specific exposure-outcome pairs, accounting for 17.6% to 25.6% of the total associations.

3.7. Metabolic network analysis of mediator metabolites

Owing to the larger number of mediator metabolites identified for hyperTC and hyperLDL-C, metabolic networks centered on the citric acid cycle were constructed for these two outcomes, thereby allowing a system-level visualization of the metabolic perturbations (Fig. 5 and S11). Several pathways, including amino acid metabolism, butanoate

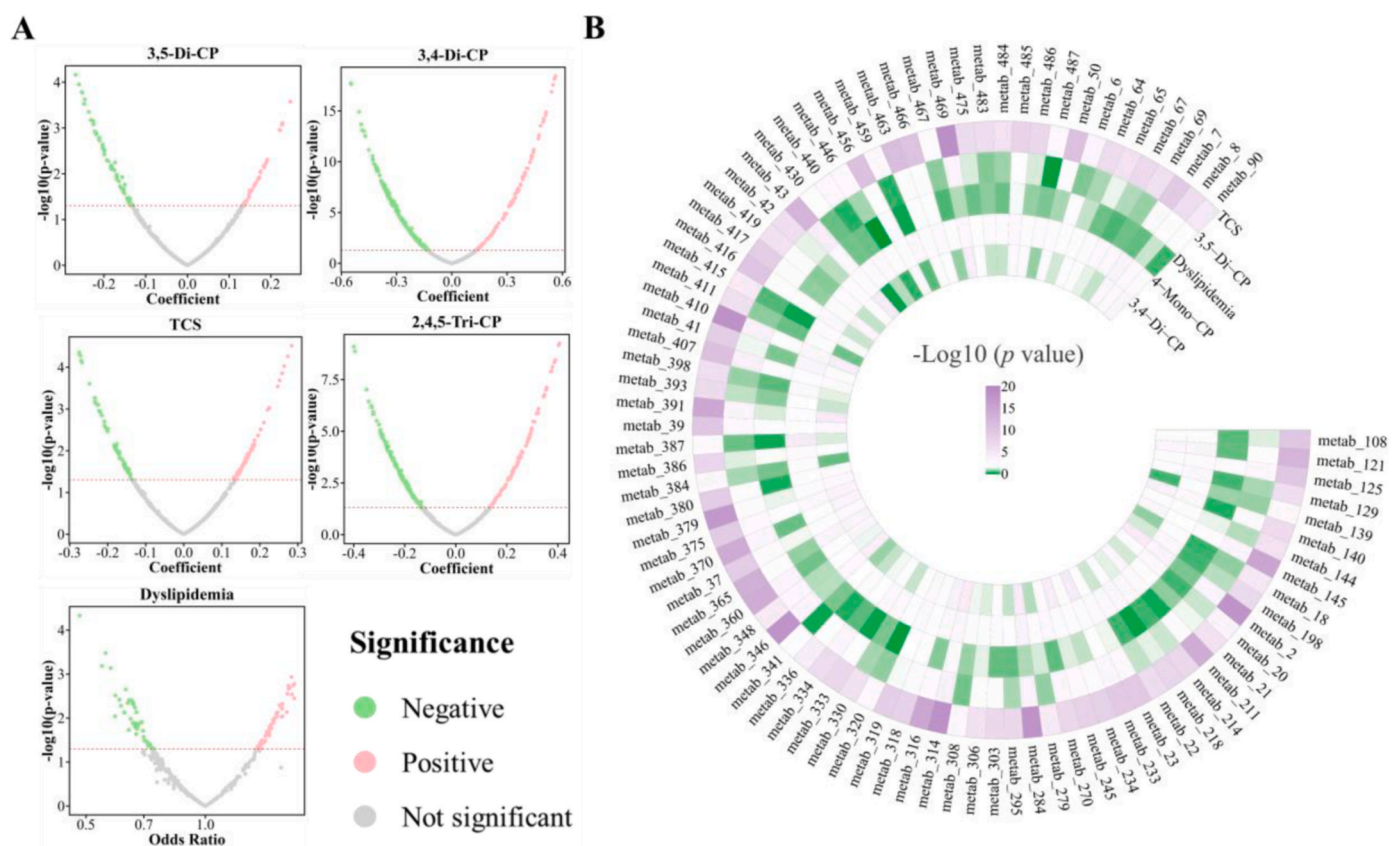


Fig. 3. MWAS of PC exposure and dyslipidemia and overlap analysis. (A) Volcano plots displaying associations of urinary PC exposures (linear regression) and dyslipidemia (logistic regression) with serum metabolites. The red dashed line indicates the statistical significance threshold ($p = 0.05$). (B) Heatmap visualizing the overlap of metabolites significantly associated with both urinary PC exposures and dyslipidemia. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)



Fig. 4. Mediation effects of enriched pathway metabolites on the associations between PC exposures and dyslipidemia and its subtypes.

metabolism, and fatty acid biosynthesis, were directly connected to the cycle, whereas retinol metabolism formed an independent module. Mapping the mediator metabolites onto the network revealed two distinct expression patterns (Fig. S12): pyruvate, creatine, N-acetyl-L-glutamate, and 4-aminobutanoate were downregulated in cases and inversely associated with exposures and outcomes according to the MWAS, while 4-hydroxy-2-oxoglutarate and 2-oxoglutarate followed the reverse trend, characterized by upregulation in cases and positive associations. Collectively, this network analysis integrates the individual mediator metabolites into a cohesive framework, revealing that the citric acid cycle serves as a central hub connecting multiple metabolic pathways, with opposing expression patterns distinguishing putatively protective metabolites from risk-associated ones.

3.8. Quantitative contributions of risk factors to dyslipidemia and its subtypes

Hierarchical partitioning analysis quantified the contributions of phenolic compounds (PCs), epidemiological factors, and their interaction term to dyslipidemia and its subtypes (Fig. 6). Together, these factors explained 11.3% of the total variance in dyslipidemia outcomes. PCs collectively contributed 4.28%, with 3,5-Di-CP as the largest individual contributor among PCs (1.61%), followed by 2,3,4,6-Tetra-CP (0.78%), 3,4-Di-CP (0.75%), and TCS (0.74%). For comparison, BMI was the largest individual contributor among epidemiological factors (1.89%), followed by occupation (0.63%) and income (0.60%). For individual lipid outcomes, all variables collectively explained 6.91% to 14.4% of the variance. PCs contributed the most to three subtypes, with 3,5-Di-CP and 2,3,4,6-Tetra-CP being the predominant contributors. In contrast, epidemiological factors contributed most to dyslipidemia, with BMI driving this effect. Notably, the interaction term between PCs and

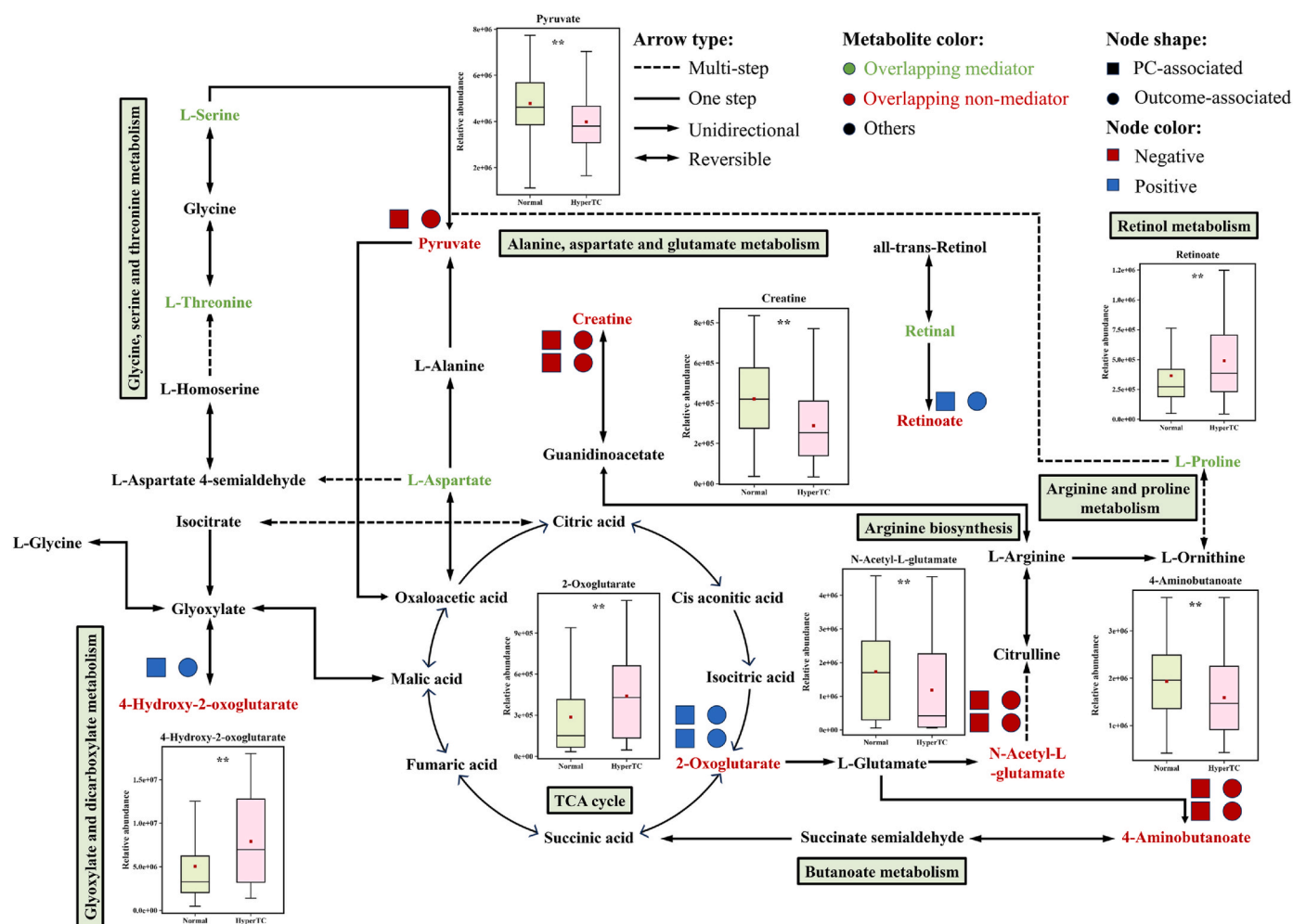


Fig. 5. Metabolic networks of enriched pathways and mediator metabolites for hyperTC. Networks were constructed with the citric acid cycle as a central hub. For metabolites with significant mediation effects, box plots display the comparison of relative abundances between disease groups and healthy controls. Statistical significance of differences between groups was assessed using the Mann-Whitney *U* test. Asterisks denote statistical significance: **p* < 0.05, ***p* < 0.01. A metabolite's count indicates the number of significantly associated PCs.

epidemiological factors consistently accounted for a substantial proportion of the explained variance across all outcomes, suggesting a synergistic rather than isolated effect of chemical exposures and host factors on lipid outcomes. In summary, these findings quantify the distinct contribution patterns of chemical exposures and host factors across lipid phenotypes, with PCs playing a dominant role in isolated lipid subtypes and BMI being more influential in overall dyslipidemia. The substantial interaction effects further highlight that PC exposure and epidemiological factors jointly, rather than independently, contribute to lipid dysregulation.

4. Discussion

In this study of e-waste workers and nearby residents, both individual and mixture exposures to specific PCs were associated with higher risks of dyslipidemia and its subtypes. Stratified analyses further suggested potential differences in these associations across population subgroups. Untargeted metabolomics identified metabolic alterations associated with both PC exposure and dyslipidemia, providing insights into the potential pathways underlying the observed associations. Hierarchical partitioning analysis further estimated the relative contributions of PC exposure, conventional epidemiological factors, and their shared components to variation in dyslipidemia outcomes. Collectively, these findings provide new evidence linking PC exposure to lipid

metabolic abnormalities and highlight the need for integrated strategies addressing HPs, BPs, their precursors, and other modifiable risk factors to reduce the cardiovascular health burden among e-waste workers and nearby residents.

We observed significant associations between TCS exposure and elevated risks of dyslipidemia and its subtypes in e-waste workers and nearby residents, which align with prior epidemiological studies. For instance, a study conducted in Shenzhen involving 1282 elderly residents found positive associations between TCS exposure and hyperTC (OR = 1.17) as well as hyperLDL (OR = 1.35), indicating that even in a general community setting, TCS may contribute to adverse lipid profiles (Guo et al., 2024). Similarly, analysis of the United States National Health and Nutrition Examination Survey (US NHANES) data from over 3000 participants reported positive associations between urinary TCS concentrations and total cholesterol and LDL-C levels, with significant dose-response relationships observed across exposure quartiles (Nasab et al., 2021). Another large-scale investigation in China, which included more than 6000 adults from a chronic disease cohort, linked TCS exposure to increased odds of hyperlipidemia (OR = 1.38), further supporting the consistency of this association across different populations and geographic regions (Zheng et al., 2026). Experimental evidence supports results in the present research. Experimental studies provide additional support for the observed associations. In vitro exposure to TCS promoted lipid accumulation and increased triglyceride

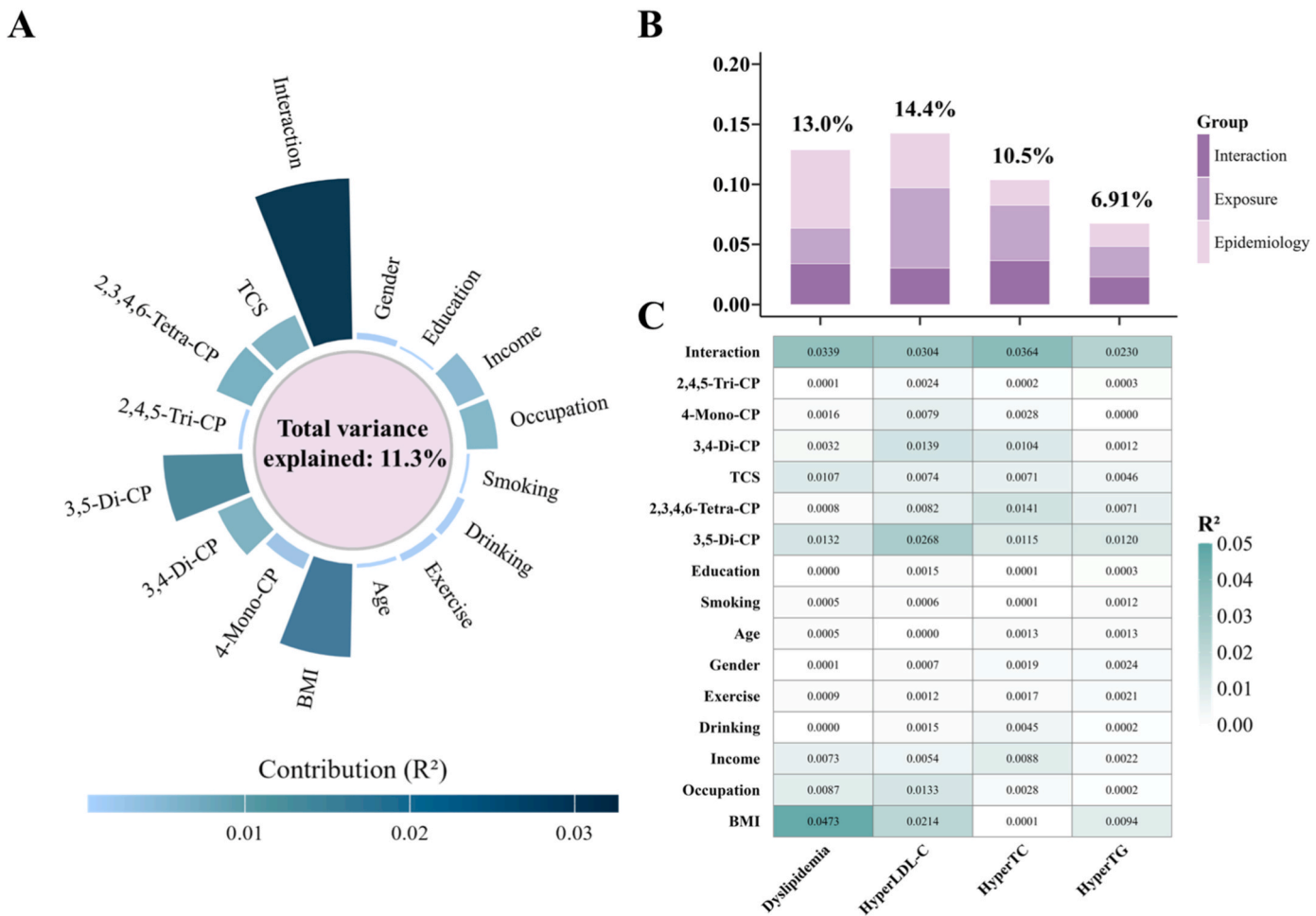


Fig. 6. Hierarchical partitioning analysis quantifying the contributions of PCs and epidemiological factors to dyslipidemia and its subtypes. (A) Circular bar plot showing the contribution of each variable to the total explained variance across all dyslipidemia outcomes. (B) Stacked bar chart illustrating the total explained variance per outcome, decomposed into three factor groups: epidemiological factors, PCs, and their interaction. (C) Heatmap displaying the contribution of each variable to each outcome.

and total cholesterol levels in human hepatocytes and adipocytes in a dose-dependent manner (An et al., 2023). Similarly, a zebrafish study showed that TCS induced lipid accumulation in the liver and intestine, potentially through activation of the PPAR γ pathway and modulation of m6A RNA methylation (Li et al., 2024). In summary, our findings support TCS as a risk factor for lipid metabolism disorders, warranting stricter environmental regulation and health surveillance in e-waste recycling areas.

Epidemiological evidence linking chlorophenol exposure to lipid metabolism remains limited, with most studies conducted in general populations exposed to background environmental levels where metabolic effects may be difficult to detect. For instance, an analysis of NHANES data from 10,428 U.S. adults reported no association between 2,4-dichlorophenol and dyslipidemia outcomes (Rooney et al., 2019). A prospective study of 73 Mexican women observed positive associations between 2,5-Di-CP/2,4-dichlorophenol and hyperTG, but the confidence interval included 1, indicating statistical imprecision (Zamora et al., 2021). In contrast, the research of pentachlorophenol manufacturing workers found elevated triglyceride levels among exposed individuals, with more pronounced effects in those exhibiting chloracne (Baxter, 1984). Our results similarly revealed significant positive associations between several chlorophenol homologues, including 3,4-Di-CP, 3,5-Di-CP, 4-mono-CP, and 2,4,5-Tri-CP, and the risk of dyslipidemia outcomes in e-waste workers and nearby residents. This apparent discrepancy may largely be explained by exposure

magnitude rather than by congener-specific differences alone. Although chlorophenol congeners differ in lipophilicity and endocrine-disrupting potency depending on chlorine number and substitution pattern (Yu et al., 2019), the direction of association is likely determined by where a population falls on the dose response curve (Vandenberg et al., 2012). General populations exposed to background environmental levels may operate in a low-dose window where homeostatic compensatory mechanisms prevail, manifesting as null or inverse associations (Shi et al., 2024). By contrast, populations with high occupational or environmental exposure, such as chemical-industry workers and residents of e-waste recycling areas, may be more likely to exhibit detectable alterations in lipid homeostasis (Baxter, 1984; Song et al., 2023). This interpretation is consistent with non-monotonic dose-response relationships commonly observed for endocrine-disrupting chemicals (Vandenberg et al., 2012). Together, these findings call for greater attention to the health risks faced by occupationally exposed populations and communities near highly contaminated sites, which remain understudied in environmental health research.

Stratified analyses revealed that demographic factors such as age, BMI, and gender significantly modified the associations between PC exposure and dyslipidemia, highlighting the importance of considering individual susceptibility in risk assessment. Age exhibited a dichotomous pattern, with younger and middle-aged individuals showing greater susceptibility to 3,5-Di-CP and 3,4-Di-CP-related hyperLDL-C and hyperTC, whereas the same exposures were linked to hyperTG in

the elderly, suggesting an age-related shift in metabolic pathways affected by these PCs (Bravo et al., 1994; Spitler and Davies, 2020). BMI also served as a critical effect modifier, with positive associations between PCs and dyslipidemia or hyperTC being more pronounced in normal-weight individuals than in those with overweight or obesity. This seemingly paradoxical finding may reflect that obesity-related metabolic disturbances overshadow the impact of PC exposure, whereas in normal-weight individuals, PCs may act as a more prominent initiating factor for lipid dysregulation (Bennett et al., 2025). Associations of 3,5-Di-CP and 3,4-Di-CP with dyslipidemia and hyperTC appeared more pronounced among males than among females. These patterns may reflect gender-related differences in xenobiotic metabolism, hormonal regulation, or hepatic lipid handling, although the underlying mechanisms remain unclear (Morán-Costoya et al., 2021; Palumbo et al., 2025; Robinson et al., 2021). Collectively, these findings underscore the necessity of incorporating demographic factors into risk assessment frameworks for PCs.

In the WQS analysis, 3,4-Di-CP contributed the largest weight to hyperTC, whereas its contribution to hyperLDL-C was relatively small. This outcome-specific pattern may indicate that 3,4-Di-CP is more closely related to overall cholesterol homeostasis or non-LDL cholesterol fractions than to LDL-C specifically (Quispe et al., 2020). TC reflects cholesterol carried by multiple lipoprotein fractions, whereas LDL-C represents a more specific cholesterol component (Schmidt et al., 2023). Thus, the stronger contribution of 3,4-Di-CP to hyperTC may reflect a broader association with cholesterol dysregulation rather than an effect limited to LDL-C. Notably, although 3,4-Di-CP was not the dominant contributor to all lipid outcomes, its WQS weights exceeded 10% across other dyslipidemia-related phenotypes, suggesting a potentially consistent but outcome-dependent contribution to the lipid-related mixture effect. Thus, future longitudinal studies, external population validation, and mechanistic investigations are needed to determine whether 3,4-Di-CP is differentially associated with various lipoprotein fractions and to clarify its potential involvement in cholesterol dysregulation.

We identified nine metabolites that mediated the associations between PC exposure and dyslipidemia (and its subtypes), with these metabolites primarily involved in amino acid, energy, and retinol metabolism. Several key metabolites, including N-Acetyl-L-glutamate, creatine, pyruvate, and 4-aminobutanoate, were consistently down-regulated across multiple PC-disease associations. N-Acetyl-L-glutamate serves as an activator of mitochondrial urea cycle enzymes, and its reduction may reflect impaired nitrogen disposal and mitochondrial function (Magnifico et al., 2018; Qiu et al., 2025). The decreased levels of creatine and pyruvate point to potential deficits in cellular energy buffering and glycolytic flux (Nault et al., 2016; Ostojic and Rátgéber, 2025). Reduced 4-aminobutanoate, a neurotransmitter involved in hypothalamic energy balance that is synthesized via citrate cycle-dependent glutamate conversion, suggests possible disruption of mitochondrial metabolism and neuroendocrine signaling (Kölker, 2018; Zhang et al., 2024b). Concurrently, retinol metabolism operated as an independent module, with retinal and retinoate consistently associated with dyslipidemia, suggesting that PCs may also act through parallel nuclear receptor signaling pathways such as RAR/RXR to influence lipogenesis (Chambon, 1996; Li et al., 2021). Collectively, these findings point to a multi-faceted disruption of metabolic homeostasis and identify specific metabolite nodes that may serve as early biomarkers and potential targets for intervention in PC-associated lipid disorders.

While a core set of metabolites was shared across outcomes, the mediation landscape was distinctly modulated by dyslipidemia subtype. In hyperLDL-C, the metabolic network was centered on 4-aminobutanoate, creatine, 2-oxoglutarate, and pyruvate, implicating disruptions in butanoate metabolism and arginine/proline metabolism in LDL particle regulation. In contrast, hyperTC exhibited a broader and more complex signature, uniquely involving glycine, serine, and threonine metabolism alongside the glyoxylate and dicarboxylate pathway.

Notably, unlike the predominantly decreased metabolites observed across other associations, 4-hydroxy-2-oxoglutarate and 2-oxoglutarate were elevated in hyperTC cases, suggesting a distinct metabolic pattern that may involve oxidative stress and mitochondrial dysfunction via the hydroxyproline degradation pathway (Riedel et al., 2012; Wanders et al., 2025). This dualistic metabolic response, characterized by decreased levels of energy-related metabolites alongside elevated levels of certain oxidative stress markers, highlights the subtype-specific nature of PC-related metabolic disruption. The convergence of multiple PC exposures on these specific metabolites underscores their potential as biomarkers for early effect monitoring and as subtype-specific targets for mitigating environmentally induced lipid disorders (Mato et al., 2019). Future studies should validate these findings in experimental models and explore whether dietary modulation (e.g., creatine or arginine supplementation) can mitigate PC-associated dyslipidemia in a subtype-specific manner.

Hierarchical partitioning quantitatively decomposed the variance in the outcomes of interest, attributing contributions to individual influencing factors and their interactions, thus providing insights beyond simple association (Cao and Wang, 2023). After accounting for all measured variables, we found that PC exposure explained 4.28% of the variance in dyslipidemia outcomes. In the context of the e-waste exposure, where thousands of coexisting pollutants and numerous host factors simultaneously contribute to health outcomes, this proportion represents a detectable and biologically meaningful signal rather than a negligible one (Chen et al., 2022). Notably, this 4.28% is comparable to the proportion of variance attributable to conventional risk factors such as BMI and lifestyle in similar settings, underscoring that even a modest explained variance from a single chemical class can identify priority pollutants relevant to disease risk. Additionally, the interplay between PC exposure and epidemiological factors explained 3.26% of the variance in dyslipidemia outcomes, a proportion similar to that of chemical composition independently. This suggests a synergistic effect where the impact of PCs on lipid abnormalities may be amplified by host characteristics like BMI, occupation, and income. A previous study reported that residents in e-waste recycling areas may experience a disproportionate increase in disease risk due to the interaction of high chemical exposure and socioeconomic disadvantage (Eckhardt and Kaifie, 2024). A review of 58 e-waste studies further indicated that, beyond chemical exposure, workers face additional risks related to low income, limited education, and low health literacy, which are often overlooked in occupational health research (Liu, 2023). Collectively, hierarchical partitioning provides evidence that PCs are associated with adverse lipid metabolism in e-waste workers and nearby residents and highlights the need to account for the combined effects of chemical exposure and epidemiological factors when designing risk reduction strategies.

Several strengths of this study warrant consideration. First, the study population was recruited from an e-waste recycling area, a setting that provides a natural high exposure scenario and offers a unique opportunity to examine exposure-outcome associations. Second, hierarchical partitioning analysis was employed to quantitatively decompose the explained variance of lipid abnormalities into contributions from individual PCs, epidemiological factors, and their interaction, thereby providing a layer of inference beyond traditional association and mixture analyses. Third, a metabolomics framework was used to identify key pathways and metabolites linking PC exposure to dyslipidemia, offering a systems-level perspective for understanding the underlying mechanisms. Several limitations should also be acknowledged. The cross-sectional design precludes causal inference, and reverse causality cannot be entirely ruled out despite the biological plausibility of the observed associations. While hierarchical partitioning analysis effectively quantifies the relative importance of predictors, it has inherent limitations. In particular, this study did not measure other major pollutants associated with e-waste beyond HPs and BPs, such as heavy metals, polychlorinated dibenzo-p-dioxins/dibenzofurans, and other flame retardants. Thus, their potential confounding effects on the

observed lipid abnormalities cannot be ruled out. Additionally, although we identified several key metabolites as potential mediators, functional validation in experimental models is needed to confirm their causal roles and elucidate the underlying molecular mechanisms.

5. Conclusion

This study demonstrated that exposure to specific PCs and their mixture is associated with elevated risks of dyslipidemia and its subtypes among e-waste workers and nearby residents, with age, BMI, and gender as effect modifiers. Nine metabolites involved in amino acid, energy, and retinol metabolism were identified as key mediators, accounting for 14.8% to 63.7% of the observed associations. Furthermore, PC exposure alone explained 4.28% of the variance in lipid metabolism, indicating its important role in driving lipid metabolism abnormalities. Our findings reveal the metabolic mechanisms linking PC exposure to dyslipidemia and underscore the need for integrated strategies targeting PC pollution and other traditional risk factors to reduce the burden of lipid disorders in e-waste workers and nearby residents. Future research should prioritize longitudinal cohort studies to establish causal links and experimental models to validate the functional roles of the identified mediator metabolites, thereby providing a solid foundation for targeted interventions.

CRediT authorship contribution statement

Meng-Yang Li: Writing – original draft, Methodology, Investigation, Formal analysis. **Hong-Xuan Kuang:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Formal analysis. **Tian-Hong Chen:** Methodology, Investigation, Formal analysis. **Xiu-Fei Wang:** Investigation. **Yin-Fei Song:** Investigation. **Ming-Deng Xiang:** Investigation. **Ying-Xin Yu:** Writing – review & editing, Supervision. **Yun-Jiang Yu:** Writing – review & editing, Supervision.

Ethics declaration

Written informed consent to take part in the study and to publish the article has been obtained from all participants or their legal representatives. The privacy rights of participants have been observed.

This study included organ or tissue donors. This study includes human biological material and consent was obtained by donors, or their next of kin or legal representatives, for use in this study and for publication of the article. The samples used in this research were not sourced from executed prisoners or prisoners of conscience.

This study was performed in compliance with relevant laws, regulatory frameworks and guidelines where the research took place. This study was approved by the Research Ethics Committee of South China Normal University. (Approval No. SCNU-SLS-2016-001)

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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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.envpol.2026.129065>.

Data availability

The authors do not have permission to share data.

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