



Triglyceride profiles are associated with subacute exposure to bisphenol A in healthy young adults

Xinchen Lu^{a,1}, Yan Lin^{b,1}, Xinghua Qiu^{a,*}, Jinming Liu^a, Tong Zhu^a, Jesus A. Araujo^{b,c}, Oliver Fiehn^d, Yifang Zhu^{b,*}

^a State Key Joint Laboratory for Environmental Simulation and Pollution Control, College of Environmental Sciences and Engineering, Center for Environment and Health, Peking University, Beijing 100871, PR China

^b Department of Environmental Health Sciences, Jonathan and Karin Fielding School of Public Health, University of California Los Angeles, Los Angeles, California 90095, United States

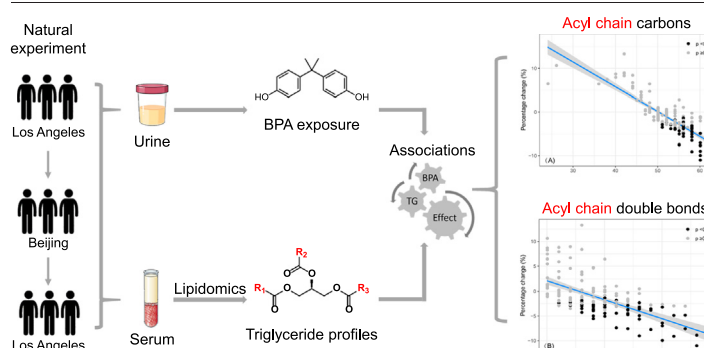
^c Division of Cardiology, Department of Medicine, David Geffen School of Medicine at University of California Los Angeles, Los Angeles, California 90095, United States

^d NIH-West Coast Metabolomics Center, University of California, Davis, 451 Health Sciences Drive, Davis, CA 95616, United States

HIGHLIGHTS

- We studied the effect of real-world BPA exposure with a natural experiment
- Triglycerides were found the major BPA-associated lipids through lipidomic approach
- Changes of triglyceride profile suggested cardiometabolic effect associated with BPA
- BMI modified the associations between triglyceride profile and BPA exposure

GRAPHICAL ABSTRACT



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ABSTRACT

Conflicted results from previous epidemiological studies call for mechanistic evidence to associate exposure to bisphenol A (BPA) with cardiometabolic diseases. In this natural experiment among healthy travelers from Los Angeles (LA) to Beijing, we collected paired urine and blood samples before their departure, 6–8 weeks after their arrival to Beijing, and 4–7 weeks after their return to LA for the assessment of urinary BPA and lipidome in the serum fraction of blood, to study the effects of drastically changed BPA exposure on the lipid metabolism in relation to the development of cardiometabolic disorders. We used linear mixed-effects models with random intercepts for participant and phase to examine the associations between urinary BPA and serum lipidome. Among 744 lipid species from seven classes, triglyceride (TGs) species showed the strongest associations with BPA exposure. The elevation in BPA exposure was associated with increases in TGs with short carbon chains or few double bonds, and decreases in TGs with long carbon chains or many double bonds. A significant linear relationship was observed between BPA-associated TG changes and the number of carbons and double-bonds in the acyl chain. No modification effects of gender but of body mass index (BMI) were observed on the associations between BPA exposure and TGs. This interdisciplinary environmental research substantiated the cardiometabolic effects of BPA according to the perturbations of TG profiling.

* Corresponding authors.

E-mail addresses: xhqi@pku.edu.cn (X. Qiu), yifang@ucla.edu (Y. Zhu).

¹ These authors contributed equally.

1. Introduction

Environmental contaminants in the form of either by-products from combustion processes or additives from industrial products, pose a significant public health risk globally. Bisphenol A (BPA) is one of the world's most extensively produced chemicals and is widely used as the monomer in polycarbonate and epoxy resin (Mustieles et al., 2020). Due to its ubiquitous presence in items used in daily-life as well as environmental media distributed in multiple-spheres, BPA could enter human body through multiple pathways and has been frequently detected in biological samples from humans (Liu and Martin, 2017). For example, in the National Health and Nutrition Examination Surveys (NHANES), urinary BPA was detected in over 90% of samples (Calafat et al., 2005), with average levels from 2.21 to 6.10 ng/mL in adults and from 2.97 to 4.89 ng/mL in children throughout the six NHANES cycles (Dunder et al., 2019).

There have been public health concerns regarding the safety of the commercial use of BPA in food containers and packaging, with the debate continuing even after the United States Food and Drug Administration (US FDA) concluded the safety of BPA at current low levels (Vandenberg et al., 2019). Remarkably, an increasing number of epidemiological studies, mostly with a cross-sectional design, have associated BPA exposure with cardiometabolic disorders, including cardiovascular diseases (Lang et al., 2008), type 2 diabetes mellitus (T2DM; Sowlat et al., 2016), obesity (Hao et al., 2018), and non-alcoholic fatty liver disease (Kim et al., 2019), which is supported by in vitro and in vivo studies with BPA exposure at environmentally relevant levels (Alonso-Magdalena et al., 2011; Hugo et al., 2008; Zhang et al., 2020). However, some other epidemiological studies have failed to detect significant associations (Kim and Park, 2013; LaKind et al., 2012; Ning et al., 2011), and the inconsistency may be, at least partially, derived from exposure misclassification due to the single measurement of BPA in cross-sectional studies. Consequentially, concrete evidence is lacking as to whether BPA causes adverse cardiometabolic health effects.

Lipids play a key role in the progression of cardiometabolic disorders (Meikle et al., 2014). The dysregulation of adipose lipolysis and elevated release of fatty acids from triglycerides (TGs) could initiate insulin resistance and increase the risk of T2DM and other cardiometabolic diseases through multiple mechanisms, including increased oxidative stress, the activation of protein kinase C, and proinflammatory pathways (Boden et al., 2005; Denhez et al., 2020; Meikle et al., 2014). Dysfunctional lipid metabolism, especially cholesterol metabolism, could also promote plaque instability and rupture, and therefore contribute to the incidence of atherosclerotic cardiovascular disease (Meikle et al., 2014). Total TG and total cholesterol have been used as an index for clinical diagnoses, and emerging lipidomic approaches provide the opportunity to examine more lipid classes as well as detailed molecular species and improve our understanding of the pathophysiology of cardiometabolic diseases. Therefore, we hypothesized that lipids could also offer an insight into the early cardiometabolic effects associated with BPA exposure. Although some epidemiological studies have investigated the associations between BPA and total TG, they have produced conflicting results (Dunder et al., 2019; Wang et al., 2020), which is presumably attributable to the reliance on the total amounts of lipid classes. To address this issue, we applied lipid profiling in this study to characterize the cardiometabolic effects after BPA exposure.

In our previous study, we conducted a natural experiment on healthy young adults, who traveled from Los Angeles (LA) to Beijing, to investigate the early cardiovascular effects of air pollution exposure (Lin et al., 2019). Interestingly, among this population group we observed higher urinary BPA levels in Beijing than in LA probably due to different regulation policies and behavioral patterns in two cities (Lin et al., 2020), which provided a unique quasi-experimental opportunity to further study the health effects induced by BPA exposure. Applying a lipidomic approach to serum samples from this novel designed study, we extended the previous study from exposures to health effects. The aim of this study is to: (1) investigate the association of BPA exposure and lipidome, and (2) check if such associations were related to lipid structure and reflected cardiometabolic effects.

2. Methods

2.1. Study design and sample collection

As reported previously (Lin et al., 2019), we recruited 26 students from an international exchange program between the University of California, Los Angeles (UCLA) and Peking University (PKU) in 2014 and 2015. Students from UCLA traveled to and stayed in Beijing for 10 weeks. All the participants were over 18 years old and had no history of smoking, cardiometabolic diseases, or chronic inflammation during the previous six months. The study was approved by the institutional review boards of both UCLA and PKU. All participants signed a written consent form upon enrollment.

For each participant, we collected paired urine and peripheral blood samples in three phases: 1–3 weeks before departure (LA-before); 6–8 weeks after arrival (Beijing); and 4–7 weeks after returning to LA (LA-after). All these samples were collected in the morning between 8 and 10 a.m. after fasting for at least 8 h to minimize potential effects of circadian rhythms and diets. The serum fraction was separated from whole peripheral blood after 1-hs stabilization and 15-mins centrifugation at 3000 rpm. An additional 5–7 urine samples were collected every 1–4 weeks to evaluate the exposure levels during the whole experiment period. The participants were required to fast for at least 8 h before sampling to minimize any potential dietary effects. The serum fraction (~1 mL) was aliquoted and immediately stored in -80°C before instrumental analyses.

2.2. Instrumental analyses

A 20 μL aliquot of each serum sample was used for lipidomic assessment. Briefly, samples were randomized to minimize the potential batch effect from storage. A solvent mixture of methanol and methyl tertiary-butyl ether (MTBE; 225/750 μL) was added, followed by vortexing for 10 s and shaking for 5 min. Liquid chromatography-mass spectrometry (LC-MS) grade water (188 μL) was then added and the mixture was vortexed for 20 s to induce phase separation. After centrifuging at 14,000 rpm for 2 min, 350 μL solvent from the upper layer extract was taken and evaporated to dryness with a CentriVap vacuum concentrator (Labconco Corporation, Kansas City, MO, USA). The dried extracts were resuspended with 90 μL 9:1 methanol/toluene (v/v), and then analyzed by ultrahigh performance liquid chromatography-quadrupole (UHPLC-Q) orbitrap mass spectrometer (Vanquish-Q Exactive HF Orbitrap MS; Thermo Fisher Scientific, Waltham, MA, USA) with an electrospray ionization (ESI) source at both the positive and negative ionization modes. An Acquity CSH C18 column (2.1 mm i.d., 100 mm length, 1.7 μm particle size; Waters Corporation, Milford, MA, USA) was applied for separation. Quality control (QC) samples, pooled from all serum samples (Dunn et al., 2011), were analyzed every 10 samples. The mass spectrometer was operated in data-dependent acquisition mode: MS1 mass resolution of 60,000; data-dependent tandem mass spectrometry (dd-MS/MS) with four scans per cycle; dd-MS/MS resolution of 15,000; and normalized collision energy at 20/30/40 V. To increase the coverage, we generated MS/MS exclusion lists with the iterative exclusion (IE-omics) algorithm (Koelmel et al., 2017) and ran four additional iterative cycles.

After the acquisition of raw data, we extracted features in MS-Dial (Tsugawa et al., 2015) and kept those with a coefficient of variation (CV) in QC samples of <30%. The intensity of the features was normalized with the systematic error removal using a random forest (SERRF) algorithm to remove systemic variations (Fan et al., 2019). The features were identified to specific lipids with the MS/MS spectra and retention indices in the LipidBlast library (Kind et al., 2013). Details of the lipidomics procedure are provided as supporting information.

The concentration of urinary BPA metabolites and estimated daily intakes (EDI, $\mu\text{g}/\text{kg}$ body weight/day) coupled with 72 serum samples were obtained from our previous study (Lin et al., 2020). Urinary BPA was measured by gas chromatography-mass spectrometry (GC-MS; 7890A-5975C, Agilent Technologies, Santa Clara, CA, USA) after methylation with

diazomethane as described previously (Lin et al., 2020). Concentrations of BPA were normalized with urinary creatinine. The EDI were calculated with the following model (Lin et al., 2020):

$$EDI = C_u \times V_u \times \frac{1}{W}$$

where C_u is the unadjusted BPA level ($\mu\text{g/mL}$), V_u is the urine excretion rate (L/day), and W is the body weight (kg). Urine excretion rates were assigned as 1.6 and 1.2 L/day for males and females, respectively (Lin et al., 2020).

2.3. Statistical analyses

The percentage change in lipid levels associated with urinary BPA was estimated by a linear mixed-effect model with random intercepts for both participant and phase to control individual difference and the confounders that might differ among three phases (i.e., LA-before, Beijing and LA-after). Food related metabolites (i.e., caffeine, theobromine, proline betaine, and vitamin E) and polycyclic aromatic hydrocarbons (PAHs) were further controlled in the sensitivity analysis. The estimated β and p -values were applied for the enrichment analysis to profile the associations between urinary BPA and serum lipid classes. We first annotated all the lipids into various classes according to their chemical structures and further calculated the lipid class-level p -values with the Kolmogorov–Smirnov (KS) test. The enrichment analysis was based on the ChemRICH algorithm (Barupal and Fiehn, 2017). All the statistical analyses were performed in R with the *lme4* and *lmerTest* packages.

3. Results

3.1. Higher urinary BPA in Beijing

This study involved 26 participants (12 males and 14 females) with an age of 23.8 ± 5.6 years (average $\pm$ standard deviation) and body mass index (BMI) of $21.6 \pm 2.4 \text{ kg/m}^2$. No participants reported any history of cardiometabolic diseases, symptoms of asthma, blood coagulation disorders, rheumatological diseases, or chronic inflammation in the six months prior to the study.

During the study period, the median urinary BPA in Beijing was 2.23 (interquartile range, IQR: 1.00–3.25) $\mu\text{g/g}$ creatinine, while the values in LA-before and LA-after were 0.40 (IQR: 0.21–0.90) and 0.58 (IQR: 0.33–0.84) $\mu\text{g/g}$ creatinine, respectively (Fig. S1; Lin et al., 2020). The EDIs of BPA in Beijing and LA were respectively 59.0 (IQR: 31.4–131)

and 12.6 (IQR: 6.8–27.6) ng/kg body weight/day, calculated from the previous reported dataset (Lin et al., 2020).

3.2. Lipids associated with urinary BPA

We identified a total of 744 lipid species, and the major classes with >10 congeners are shown in Fig. S2. By combining the significant results from the linear mixed-effect model and enrichment analysis based on ChemRICH, TGs were found to be the major class associated with urinary BPA compared with other lipid classes (Fig. 1A), among which species with more acyl chain carbons or more double bonds (i.e. higher degree of unsaturation) were altered the most (Fig. 1B).

3.3. TG profiling

Because TGs were the most abundant lipids that were significantly associated with BPA exposure, the percentage change of each TG in association with urinary BPA changes was estimated based on the linear mixed-effect model. As shown in Fig. 2, although not all the TG species correlated significantly with urinary BPA, the percentage change displayed a down-sloping pattern with the increase in total acyl chain carbon number (Fig. 2A) or double bond content (Fig. 2B). In another word, TGs with few acyl-chain carbons or double bonds increased while TGs with more acyl-chain carbons or double bonds decreased. In particular, TGs with a higher acyl chain carbon number and double bond content were significantly downregulated the most with urinary BPA. With a one-fold increase in the urinary BPA level, the median percentage change of these TGs was -4.7% (IQR: -5.1 – -0.25%). No modification effects of gender but of BMI were observed on the associations between BPA exposure and TGs (Fig. 2C). This pattern still existed after controlling for other exposures, including PAHs and dietary factors, as covariates, indicating the robustness of the associations (Fig. S3). Moreover, TGs with a higher acyl chain carbon number and double bond content were more likely to decrease after participants' arrival in Beijing (Figs. S4 and S5).

4. Discussion

In this natural experiment, participants were exposed to markedly higher levels of BPA after traveling from Los Angeles to Beijing, possibly due to more strict regulation policies in the US than those in China as reported by our previous study (Lin et al., 2020). In this study, we took advantage of repeated measurement to achieve accurate evaluation on personal total exposure to BPA from multiple-spheres and complicated pathways,

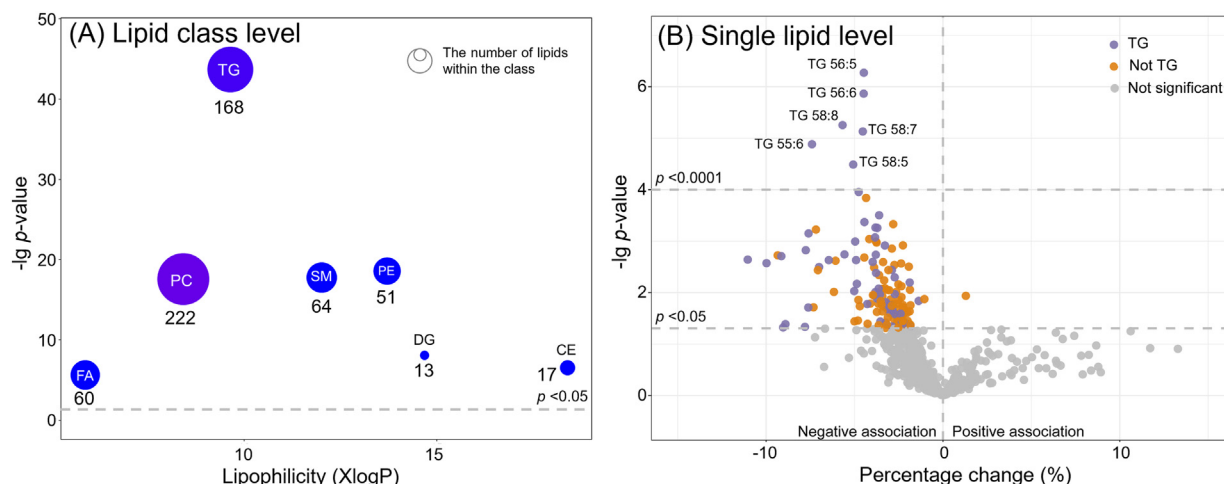


Fig. 1. Enrichment analysis on lipid class level (A) and the volcano plot on single lipid level (B) based on the statistical significance in associations of lipids with urinary BPA. TG, PC, FA, SM, PE, DG, and CE indicate triglyceride, phosphocholine, fatty acid, sphingomyelin, phosphatidylethanolamine, diglycerides, and cholesterol ester, respectively. In panel A, the median lipophilicity in the form of XlogP of each class was applied. The p -value is from a Kolmogorov–Smirnov test in the enrichment analysis. In panel B, the percentage change is that of a lipid associated with a one-fold increase in urinary BPA from a linear mixed-effect model, together with the p -value.

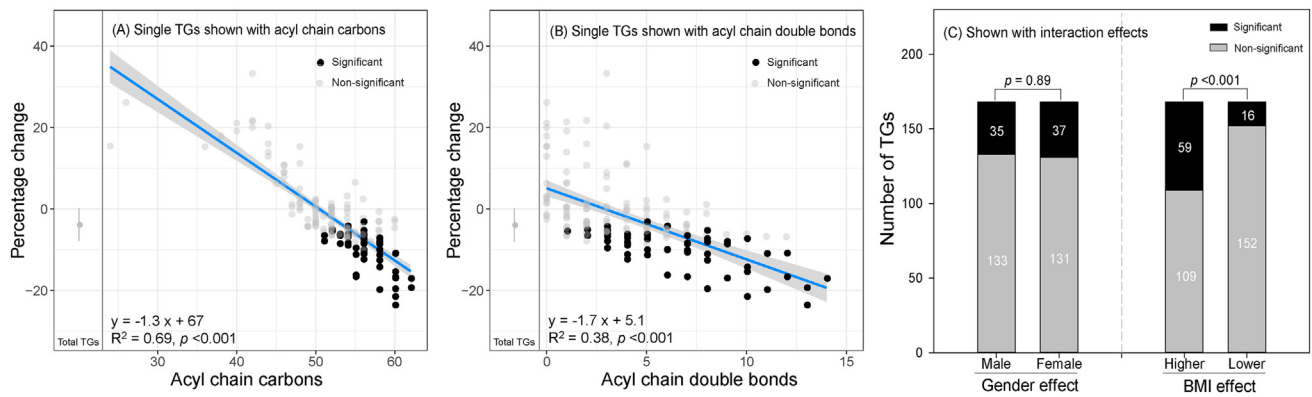


Fig. 2. Percentage change of TGs associated with a one-fold increase of urinary BPA from linear mixed-effect models, shown as a function of the number of acyl chain carbons in TGs (A), or the number of acyl chain double bonds in TGs (B); and the interaction effects due to gender or BMI (C). In panels A and B, the black points indicate TGs significantly associated with BPA ($p < 0.05$ from linear mixed-effect models) while the grey points indicate TGs not significantly associated with BPA ($p \geq 0.05$). In panel C, the Y-axis indicates the numbers of BPA associated TGs (black) and non-associated TGs (grey) in the interaction analysis. There were 12 males and 14 females in the study. P-values were obtained from Chi-square tests.

which allow us to detect significant and robust associations between BPA exposure and TG. We found that the BPA-associated TG changes exhibited a down-sloping pattern with longer carbon chains and more double bonds, which was previously found to associate with T2DM and cardiovascular diseases (Rhee et al., 2011; Suvitaival et al., 2018; Toledo et al., 2017). These results substantiated the cardiometabolic effects of BPA exposure at environmentally relevant doses from the perspective of the lipidome.

Hypertriglyceridemia is a recognized risk factor of cardiometabolic diseases. However, the overall lipid classes parameters (e.g., total TG) used in clinical diagnoses only provide a narrow snapshot for lipid metabolism. At this point, the lipid profiling might aid in a clinical risk assessment to indicate early effects before observable changes in total lipids. In humans, lipidome-based case-control studies have shown that the fold changes of TGs between T2DM and controls (Rhee et al., 2011), or the changes between the progressors and non-progressors of T2DM (Suvitaival et al., 2018), display a decreasing pattern with the increase in their acyl chain carbon number or double bond content. TGs with low carbon numbers and few double bonds have been reported to be linked with an increased risk of T2DM, while TGs with high carbon numbers and many double bonds were associated with a decreased risk. Similar results were observed for cardiovascular disease (CVD; Toledo et al., 2017). Such down-sloping pattern in TG profiling (i.e., TGs with few acyl-chain carbons or double bonds increased with BPA exposure while TGs with more acyl-chain carbons or double bonds decreased) has been proposed as an indicator of the risk of cardiometabolic diseases.

In the present study, the abovementioned cardiometabolic disease risk pattern in TGs also emerged in the associations between BPA exposure and TGs (Fig. 2A–B), substantiating the potential cardiometabolic effects of BPA exposure at environmentally relevant doses. The percentage change of TG levels with BPA exposure in general presented a linear trend. TGs with a number of acyl chain carbons of <50 or with few double bonds were positively associated with BPA exposure, while TGs with more carbon numbers or double bonds had significant negative correlations (Fig. 2A–B). Considering few studies reported BPA exposure could inhibit elongation and desaturation processes of lipids, such association were more likely to be attributed to aggravated lipolysis as well as stimulated de novo lipogenesis substantiated by previous animal studies (Szkudelska et al., 2021). As esterified constituents of TGs, saturated fatty acids (i.e., FA 16:0 and 18:0) are synthesized first, while fatty acids with more carbons and double bonds need extra elongation and desaturation processes. Such differentiated synthesis processes were more prone to increase the levels of TGs with a low number of acyl chain carbons and double bonds and therefore contribute to the linear trend in the TG profiling. Of note, we found that only negative correlations were significant, suggesting that lipolysis after BPA exposure might be more apparent than lipogenesis. Such negative

correlations might have contributed to the decreased TG levels from LA before to Beijing (Fig. S4). Furthermore, TGs with a high number of acyl chain carbons and double bonds, especially TGs 55:6, 56:5, 56:6, 58:5, 58:7, and 58:8, had the most significant associations with exposure to BPA ($p < 0.0001$; Fig. 1). Similarly, significant decrease was also observed in such TGs from LA to Beijing, comparing to the non-significant alteration in total TG (Figs. S4 and S5). They were, potentially, more sensitive biomarkers reflecting the early effects of BPA exposure on lipid metabolism.

Previous studies have documented significant gender differences in the health effects of BPA (Caporossi and Papaleo, 2015) and patterns of fat deposition, mobilization, and utilization due to the regulation of gonadal hormones (Heindel et al., 2017); however, in the present study we did not observe any modification effect of gender in the relationships between BPA exposure and each TG (Figs. 2C and S6). The significant associations of TGs with BPA exposure were not different between genders ($p = 0.89$, Chi-square test). Our results were consistent with previous epidemiological studies that had reported no gender difference in the associations between BPA exposure and T2DM (Duan et al., 2018; Rancière et al., 2019). On the other hand, although the BMI values of most participants were among the normal range, we still observed that TGs were more strongly associated with BPA exposure in participants with BMI $\geq$ median value of 21.8 kg/m² than those in participants with BMI < 21.8 kg/m² ($p < 0.001$, Chi-square test; Fig. 2C). The slopes of the fitted line of the high BMI group were significantly smaller than those of the low BMI group (i.e., $p < 0.001$ for both acyl chain carbons and double bond content), which indicated the de novo lipogenesis speed might be higher in the high BMI group (Fig. S6). This result suggested more pronounced lipolysis and lipogenesis effects of BPA exposure in participants with higher BMI, which might be partially attributed to hyperlipidemia or obesity, as high BMI might induce the abovementioned lipid perturbation effects in previous studies (Morigny et al., 2016). Therefore, higher BMI could be a risk factor aggravating the cardiometabolic effects associated with BPA exposure, i.e., individual with higher BMI might be more susceptible to BPA exposure in terms of the cardiometabolic effects. This is a new finding given that few studies have reported such susceptibility till now.

In this study, we observed significant associations between real-world exposure to BPA and altered TG profiling, even in healthy young participants, which could be attributed, at least partially, to the relatively wide range of exposure levels owing to the advantage of the natural experiment. The exposure levels of BPA in Beijing were 4.0 (95% confidence interval, CI: 2.7–6.1) times of those in LA. Such contrast could be attributed to the different regulatory policies, i.e., in the United States government and manufacturers have made extensive efforts to ban BPA from baby bottles, food packaging, and thermal paper since 2009 (Ye et al., 2015), while in China BPA was only prohibited in the production of baby bottles in 2011

(Jiang et al., 2018). However, the maximum EDI in Beijing was estimated to be 0.74 $\mu\text{g/kg}$ body weight/day calculated from the previous reported dataset (Lin et al., 2020), which was approximately two orders of magnitude lower than the reference dose of 50 $\mu\text{g/kg}$ body weight/day recommended by the US Environmental Protection Agency (EPA), and much lower than the previously established no observed adverse effect level (NOAEL; 5000–50,000 $\mu\text{g/kg}$ body weight/day; Vandenberg et al., 2019). Although the environmental exposure to BPA was much lower than the current reference dose, its potential cardiometabolic risk could not be neglected.

This study has several strengths. First, we exploited a natural experiment with significant exposure contrast in BPA exposure; Second, we conducted repeated measurements so that each participant can serve as his/her own control to reduce inter-individual variance, which was a significant advantage when compared with cross-sectional studies; Third, we have prospectively controlled the potential impacts of diet and circadian rhythm on BPA exposure to decrease the likelihood of exposure misclassification compared with retrospective studies. Admittedly, this study also has several limitations. First, although we have tried our best to recruit almost all exchange students, the sample size in this paper was smaller than that in cohort studies. Nevertheless, with the aforementioned strengths, the sample size has proven to provide enough power to detect significant associations between urinary BPA levels and lipidomic changes. Second, there are other factors that might be changed during the travel and influence or confound the associations between BPA and TGs. Therefore, our results should be considered as associative and future toxicological studies are therefore necessary to confirm the conclusion from the above epidemiological studies and further explore combined effects of multiple pollutants. Third, although previous studies have proposed associations between TG profiling and cardiometabolic effects, such associations did not necessarily indicate causal effects. A direct observation of the progression from BPA exposure to specific cardiovascular diseases would be valuable for causal inference and should be studied in future experiments.

5. Conclusion

In summary, this study focused on the interconnection of multiple spheres, specifically effects of low-dose BPA exposures at environmentally relevant levels and applied a lipidomic approach rather than total lipids for a systematic characterization of lipid homeostasis. We found the down-sloping pattern in this study that was similar to those reported in previous studies, indicating a risk of cardiometabolic diseases. We also found that TGs with a high acyl chain carbon number and double bond content were potential early biomarkers of cardiometabolic effects in healthy people. We did not find a gender difference in the associations between BPA exposure and the abovementioned TG patterns indicating cardiometabolic effects. Our study provided some insights into the cardiometabolic effects of BPA at environmentally relevant levels, and potential mediation effects associated with TGs, both of which call for a re-evaluation of BPA's current safe dose and an update to its regulatory policy.

CRediT authorship contribution statement

Xinchen Lu: Methodology, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Yan Lin:** Formal analysis, Writing – review & editing. **Xinghua Qiu:** Conceptualization, Writing – review & editing, Supervision, Funding acquisition. **Jinming Liu:** Formal analysis. **Tong Zhu:** Resources. **Jesus A. Araujo:** Resources. **Oliver Fiehn:** Resources. **Yifang Zhu:** Conceptualization, Funding acquisition.

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.scitotenv.2022.153991>.

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