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Chronic Methylmercury Exposure Induces Production of Prostaglandins: Evidence From A Population Study and A Rat Dosing Experiment

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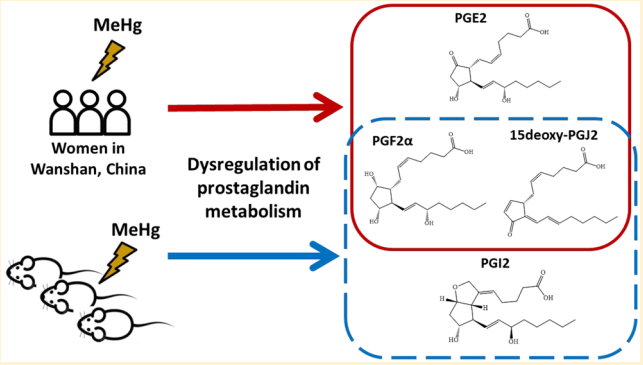
Supporting Information

ABSTRACT: Methylmercury (MeHg) is a well-known environmental neurotoxicant affecting millions worldwide who consume contaminated fishes and other food commodities. Exposure to MeHg has been shown to associate positively with some chronic diseases including cardiovascular diseases, but the mechanism is poorly characterized. MeHg had been shown to affect prostaglandin (PG) regulations in *in vitro* studies, but neither *in vivo* nor human studies investigating the effects of MeHg on PG regulations has been reported. Thus, the current study aimed to investigate the association between MeHg exposure and serum PG concentrations in a cross-sectional study among human adults followed by a validation investigation on the cause-effect relationship using a rat model. First, a total of 121 women were recruited from two cities: Wanshan and Leishan in Guizhou, China. Statistical analysis of the human data showed a positive association between blood total mercury (THg) levels and serum concentrations of PGF2α, 15-deoxy-PGJ2, and PGE2 after adjusting for site effects. In the animal study, adult female Sprague−Dawley rats were dosed with 40 μg MeHg/kg body weight/day for 12 weeks. Serum 15-deoxy-PGJ2 and 2,3*d*-6-keto-PGF1α concentrations were found to increase significantly after 6 and 10 weeks of MeHg dosing, respectively, while serum PGF2α concentration increased significantly after 12 weeks of MeHg dosing. Combined results of our human and rat studies have shown that chronic MeHg exposure induced dysregulation of PG metabolism. As PGs are a set of mediators with very diverse functions, its abnormal production may serve as the missing mechanistic link between chronic MeHg exposure and various kinds of associated clinical conditions including neurodegeneration and cardiovascular diseases.



INTRODUCTION

Methylmercury (MeHg) is a well-known environmental pollutant bioaccumulated and biomagnified to higher levels in marine fishes at high trophic levels.[1] The problem of chronic exposure to MeHg through diet has been around for decades. As recommended by the Food and Agriculture Organization of the United Nations (FAO), the provisional tolerable weekly intake (PTWI) of MeHg is 1.6 μg/kg body mass/week. Estimates of per capita mercury intake through fish consumption in a ten years survey (2001−2011) showed that 38% of the population in 175 countries had exposure higher than the PTWI.[2] In addition, consumption of MeHg-contaminated rice is another major route of exposure as it was revealed that rice paddies were active sites for methylation of inorganic Hg to produce MeHg.[3] Consumption of these rice

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and other food produce grown near areas Hg of mining and related industrial sites would lead to increased MeHg exposure.[4] As millions are exposed to MeHg continuously and its health implications are large, there is a need to document and understand the potential health impacts of chronic MeHg exposure.

Several cohort studies on populations with frequent fish consumption in the Faroe Islands, Spain, and Hong Kong were performed to investigate possible associations among abnormal physiological, behavioral outcomes, and chronic exposure to MeHg. It was shown that prenatal MeHg exposure affects cognitive functions developments in children.[5−7] However, despite these studies, potential health impacts on adults of chronic exposure to a low dose of MeHg are still unclear.[8] Cohort studies conducted in Minamata of Japan suggested that there is a casual relationship between chronic MeHg exposure and development of psychiatric symptoms among adults.[9] Others proposed that MeHg played a role in the pathogenesis of neurodegenerative diseases, as well as increasing resting heart rate and blood pressure.[10,11] Another meta-analysis showed a significant dose−response between MeHg exposure and blood pressure.[12] There is evidence suggesting the association between chronic MeHg exposure and risk of developing neurodegenerative as well as cardiovascular abnormalities. However, the mechanism is poorly characterized.

Prostaglandins (PG) are lipid autacoids derived from arachidonic acid. They sustain homeostatic functions such as modulation of blood pressure[13] and mediate pathogenic mechanisms, including the inflammatory response[14] and neurodegenerative diseases.[13] From PubMed, nine studies were reported which investigated effects of Hg/MeHg exposure on PG production. Eight reports were *in vitro* studies, mainly with brain and vascular endothelial cell cultures. It was reported that inorganic HgCl exposure increased production of arachidonic acid (AA), total PGs, thromboxane B2 (TXB2), and 8-isoprostane via activation of lipid signaling enzyme phospholipase A2 in bovine pulmonary artery vascular endothelial cells.[15] Yoshida et al. added that prostacyclin (PGI2) and prostaglandin E2 (PGE2) were released from human brain microvascular endothelial cells upon MeHg exposure.[16] Apart from *in vitro* studies, there was only one *in vivo* study which used a high concentration of $HgCl_2$ (2.5 mg/kg) to induce kidney failure in rats and was aimed to investigate the effect of agonists to PG receptors for treating chronic and acute kidney failure.[17] Effects of chronic MeHg exposure on PG regulation remain unknown.

The objective of this study is to investigate the relationship between long-term MeHg exposure and serum PG concentrations in humans and rats. We hypothesized that chronic MeHg exposure may dysregulate PG metabolism. To test this hypothesis, we conducted a cross-sectional population study on healthy women at child-bearing age who lived in two cities: Wanshan and Leishan in Guizhou Province, China. Wanshan was a historic mercury mining area in the eastern part of Guizhou Province. It was one of the largest areas of Hg mining in China and had a long history of mining activities dated back to the Qin Dynasty (~221 BC). The mining activities have resulted in severe inorganic Hg and MeHg contamination to the local freshwater system, freshwater fish and soil.[18,19] All mining activities have banned since 2001. However, residents in Wanshan are still exposed to Hg through consumption of local cultivated rice, vegetables, and poultry.[4] In contrast, Leishan has no history of Hg mining and is located in the same province; it was selected as a control site. In order to confirm the cause−effect relationship without complication induced by other confounding factors, a rat dosing study under a controlled environment was also conducted.

MATERIALS AND METHODS

Ethics Approval. All procedures dealing with human and human samples were performed in the Chinese Mainland, while all the animal work was performed in Hong Kong. All procedures on human subjects were approved by the Ethics Committee of the Affiliated Hospital of Guizhou Medical University and the Human Subjects Ethics Subcommittee of the Hong Kong Polytechnic University. All procedures on the animals were approved by The Animal Subjects Ethics Subcommittee of the Hong Kong Polytechnic University.

Human Subject Recruitment. Women (N = 74) who lived in Wanshan for at least 6 months and gave birth at local hospitals without known clinical conditions were recruited. Similarly, women (N = 47) who lived in Leishan for at least 6 months and gave birth at local hospitals without known clinical conditions were recruited. Demographic and dietary information were collected by a questionnaire. The questionnaire was designed according to guidelines from the WHO European Center for Environment and Health and modified as described in our previous study.[4] Detail descriptions for demographic and dietary survey were provided in the Supporting Information.

Collection of Whole Blood and Serum Samples. Approximately 5 mL of whole blood was collected from each participant 2−3 days before childbirth using a metal-free plastic vacutainer without anticoagulant for THg analysis. In addition, another 2 mL of whole blood per subject was collected and allowed to clot at room temperature for 30 min. The clot was removed by centrifugation at 2000 × g at 4 °C for 10 min. Serum was harvested, aliquoted, and stored at −80 °C for PG analysis. The USEPA method 1631 was adopted to quantify THg in the human whole blood. The detection limit was 0.5 ng/L and THg was detected in all samples in this study. Details of the methodology used were provided in the Supporting Information.

Quantification of Prostaglandins in Human Serum by ELISA. Serum concentrations of thromboxane A2 (TXA2), prostacyclin (PGI2), prostaglandin E2 (PGE2), prostaglandin F2α (PGF2α), and 15-deoxy-δ 12,14-prostaglandin J2 (15-deoxy-PGJ2) were quantified using ELISA assay kits purchased from Abnova (Germany). As TXA2 and PGI2 have relatively short half-lives, their serum concentrations were estimated by measuring concentrations of their stable derivatives using ELISA. The serum concentration of TXA2 was estimated by quantifying serum concentration of thromboxane B2 (TXB2, a hydrated form of TXA2). The serum concentration of PGI2 was estimated by quantifying total serum concentrations of 6-keto-prostaglandin F1α (6-keto-PGF1α) and 2,3-*dinor*-6-keto-prostaglandin F1α (2,3*d*-6-keto-PGF1α) as they are produced during PGI2 degradation. The assays were performed according to procedures recommended by the manufacturer with modifications. Details of the procedures were provided in the Supporting Information.

Animal Treatments and Serum Samples Preparations. The rat model used in this study was adopted from our previous one.[20] Sprague−Dawley (SD) rats (all female, 200−220 g, 6−8 weeks old) were housed in a controlled

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environment (20 ± 1 °C, 12 h light/12 h dark cycle). Food and water were provided *ad libitum*. Rats were randomly divided into sham, corn-oil vehicle, and MeHg groups. Each group had 12 animals. Rats in the MeHg group were fed by oral gavage with 40 μg of MeHg in corn oil/kg body weight per day. Rats fed with this dose were aimed to mimic chronic exposure to a subtoxic dose of MeHg without showing any apparent observable toxic effects. Rats in the corn-oil vehicle group were fed by oral gavage with 0.1 mL of corn oil. Rats in the sham group received the feeding procedures with neither MeHg nor corn oil administration. Biweekly body weight measurements were taken to gauge the health of these rats. For every 2 weeks until the end of the 12 weeks of MeHg administration, blood samples were collected from each rat. After collecting the blood samples, the blood samples were allowed to clot at room temperature for 30 min before being centrifuged at 2000 × *g* for 10 min at 4 °C. Serum samples were collected and apportioned into 0.2 mL aliquots and stored at −80 °C before analysis. After 12 weeks of experiment, all rats were sacrificed. THg concentrations in the rat serum samples were quantified using direct thermal decomposition coupled with atomic absorption spectrometry (MA-3000 from NIC, Japan). Details of the methodology were provided in the Supporting Information.

Sample Preparation for Untargeted Metabolomic Analysis on Rat Sera. The preparative protocol was adopted from a previous study with modifications.[21] Each 200 μL serum sample was mixed with 600 μL of ice-cold methanol before being shaken vigorously. The mixtures were allowed to stand for 15 min before being centrifuged at 13 000 × *g* at 4 °C for 10 min. Supernatants were recovered and filtered with 0.22 μm membrane. The filtrates were concentrated with a vacuum concentrator (Labconco, USA). Subsequently, the concentrates were reconstituted with 20% methanol in 0.1% formic acid (FA). Tridecanoic acid (0.5 ppm, Sigma-Aldrich, USA) was added as an internal standard. Samples for quality control (QC samples) were prepared by mixing all serum samples from the rats within the same group in equal portion. Subsequently, there were 3 QC samples in total, one from each group.

Untargeted Metabolomic Analysis. Rat serum metabolites profiles were acquired using ultra-high-performance liquid chromatography (UHPLC) coupled with dual Agilent jet stream electrospray ionization quadrupole time-of-flight mass spectrometer (Dual-AJS-ESI Q-TOF MS) (Agilent, USA). When loading into the system, a 10 μL sample was injected regularly. Reverse-phase C_{18} column (Eclipse plus C_{18} column, 150 mm × 2.1 mm i.d., 1.8 μm particle sizes) was used to separate the serum metabolites. The column was equilibrated with 0.1% FA and eluted with a linear gradient of methanol, from 5 to 80% in 30 min. The flow rate was 0.2 mL/min. Mass calibrant mix (Agilent, USA) was simultaneously injected with the eluate into the Q-TOF MS to perform real-time mass calibration. The metabolites were analyzed with both full-scan positive ion and negative ion modes separately. Detailed conditions of the Q-TOF MS were provided in the Supporting Information. The serum samples and QC samples were run in a randomized order to avoid uncertainties from an artifact-related injection order and gradual changes in the MS sensitivity along the whole analysis. Each QC sample was run in triplicates for both positive ion and negative ion MS scanning. The raw data was then analyzed using MassHunter Quantitative Analysis v. B.04.00 (Agilent, USA), subsequently with online KEGG mapper (http://www.genome.jp/kegg/tool/map_pathway2.html). Details of strategy and parameters for data analysis were provided in the Supporting Information.

PG Quantifications by Multiple Reactions Monitoring. The prostaglandin standards used in the multiple reactions monitoring (MRM) measurements were purchased from Cayman Chemical, USA. The extraction method of prostaglandins from serum samples for MRM was adopted from a previous study with modifications.[22] Briefly, one volume of serum sample was extracted with 2.5-fold volume of ethyl acetate containing 0.1% FA. The mixture was sharked vigorously for 30 s before centrifuged at 1000 × *g* at 4 °C for a minute. The upper layer was collected and dried with a vacuum concentrator (Labconco, USA). The dried extract was dissolved in 50 μL of methanol with 0.1% FA before MRM analysis. The MRM analysis was performed using UHPLC coupled with dual Agilent jet stream electrospray ionization triple quadrupole mass spectrometer (Agilent 6460, USA). Concentrated extract (10 μL) was injected into the system. Reverse-phase C_{18} column (Eclipse plus C_{18} column, 150 mm × 2.1 mm i.d., 1.8 μm particle sizes) was used to separate the prostaglandins. The column was equilibrated with 0.1% FA, and the mobile phase was ACN with 0.1% FA (B). The flow rate was 0.3 mL/min. The elution gradient started with 35% B, held for 4 min. Then, it changed linearly to 60% B at 8 min and subsequently changed linearly to 65% B at 16 min. After elution, the column was washed with 100% B for 3 min and then equilibrated with 0.1% FA. The capillary voltage and nozzle voltage for negative ion mode was set at 3.5 kV and 400 V respectively. The gas flow was 8 L/min, and the gas temperature was 300 °C. The mass transitions of PGF2α, 15-deoxy-PGJ2, and 2,3*d*-6-keto-PGF1α were summarized in Table S12. The peak area of each product ion was calculated using MassHunter Quantitative Analysis v. B.04.00 (Agilent, USA). A *t* test was used to test for the significance of any difference between groups, and the significance was set at $p \leq 0.01$.

Statistical Analysis. Pearson chi-square test was used to determine the relevance of demographic characteristics and the dietary consumption frequencies of various food items in relations to the study sites, blood THg levels as well as various serum PG concentrations. Shapiro−Wilk test was used to test for normality of the data. Since the data of human blood THg and serum concentrations of PGs were non-normal, Spearman and partial Spearman rank correlations were used to determine the correlation and significance of blood THg levels and serum concentrations of various prostaglandins with and without adjustments, respectively. The adjustments made included age, smoking and drinking habits, and aquatic food produce and freshwater fish consumption. Partial least-squares regression was performed in R using study site, blood THg level, demographic background, and dietary consumption frequencies as predictor variables as well as serum PG concentrations as dependent variables. Concentrations of PGF2a and 15-deoxy-PGJ2 were log-transformed to achieve normal distribution before the regression analysis. Lastly, in order to find if there are other previously unknown confounding factor besides MeHg that may induce prostaglandins dysregulation, directed acyclic graphs (DAG) were constructed using R. This technique was reported to have less bias in adjusting for potential confounding factors.[23] Structure of DAG was determined by a hill-climbing approach to determine the structure DAG model by the maximization of BIC (Bayesian Information Criterion) score and the detail of this approach

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Table 1. Blood THg and Serum Concentrations of PGs in Apparently Healthy Women from Wanshan (Hg Mining Site) and Leishan (Control Site)

	n	Wanshan mean	95% CI[a]	*n*	Leishan mean	95% CI	*p* value[b]
age	71[c]	25.37	(24.24, 26.49)	47	23.51	(22.08, 24.94)	0.089
blood THg, ng/mL	74	5.47	(4.77, 6.18)	47	1.47	(1.23, 1.72)	<0.001
serum PGI2, ng/mL	74	1.77	(1.28, 2.25)	47	1.17	(1.01, 1.32)	0.285
serum PGE2, ng/mL	74	3.70	(3.51, 3.89)	47	0.45	(0.27, 0.64)	<0.001
serum PGF2α, ng/mL	74	13.79	(8.43, 19.15)	47	0.33	(0.24, 0.42)	0.007
serum 15-deoxy-PGJ2, ng/mL	74	83.08	(40.49, 125.68)	47	0.74	(0.15, 1.33)	0.003

[a]Confidence intervals at a 95% confident level. [b]*t* test was used to compare means from both groups, $p < 0.01$ would be considered significant. [c]There were 3 missing data in the age category of the human subjects in Wanshan.

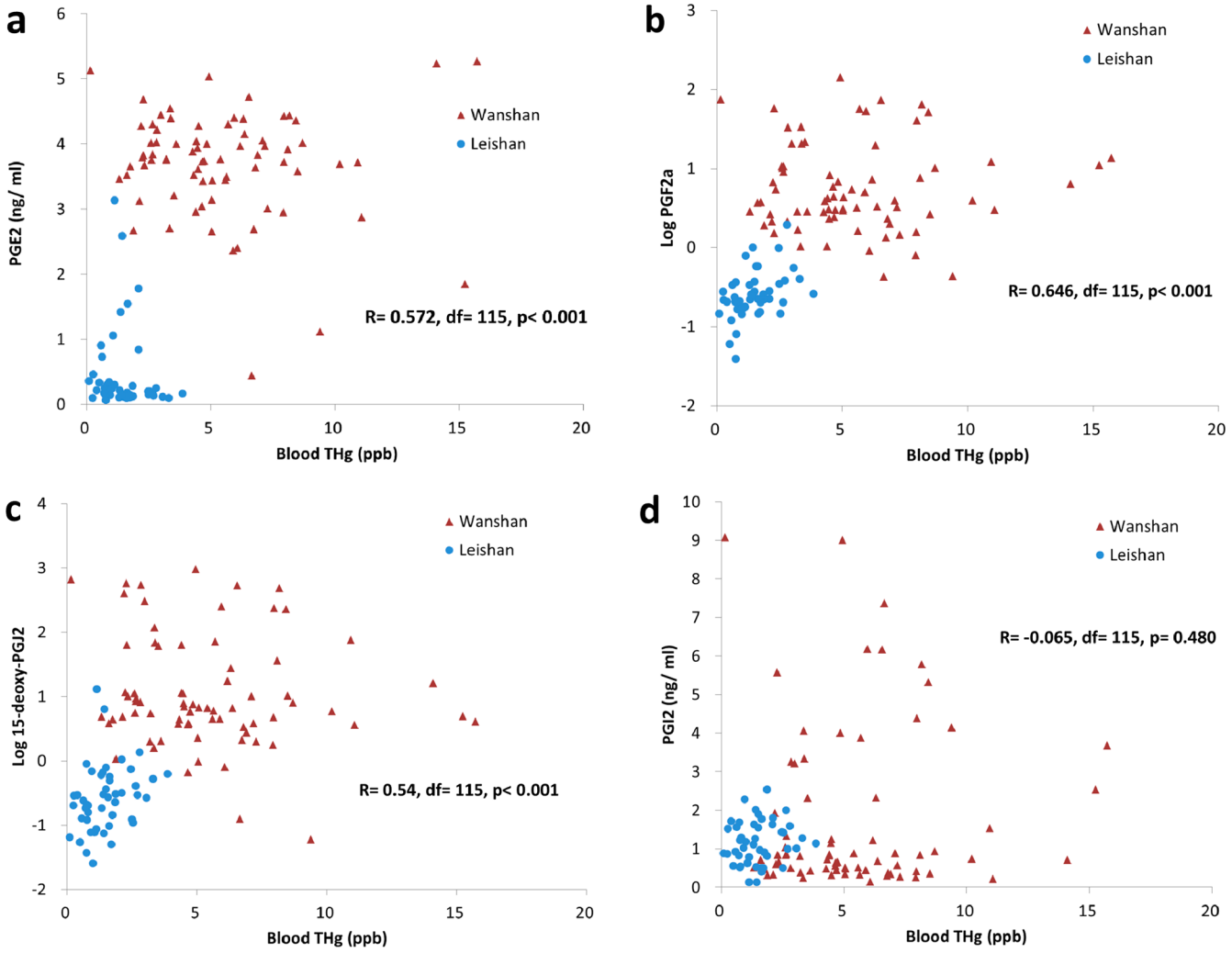

Figure 1. Correlations between blood THg and serum concentrations of PGs. The correlations between blood THg and serum PG concentrations were calculated by Spearman correlation. (a) Blood THg showed a significant and strong correlation with serum PGE2 concentration. (b and c) Blood THg showed significant and strong correlations with serum concentrations of PGF2α and 15-deoxy-PGJ2 in log scale, respectively. (d) No correlation was found between blood THg and serum PGI2 concentration. Partial Spearmen correlations between blood THg and serum concentrations of PGs with various adjustments were reported in Table S2.

has been described previously.[24] After the model structure has been decided, the parameters of DAG model are obtained by the maximum likelihood estimation, and this approach is suitable for data set with both discrete and continuous variables in this study. Relationships of variables in the DAG models were presented numerically with their conditional probability. Two-way ANOVA was used to test for the significances of increase in body weight and serum THg levels among rats in different groups. A *t*-test was used to determine the significances of relative abundances of serum metabolites among rats in vehicle group and MeHg group in the metabolomics analysis. One-way ANOVA was used to determine the significances of serum concentrations of various prostaglandins in rats from different groups quantified by ELISA. Student's *t*-test was used to determine the significances of serum concentrations of various prostaglandins in rats from the vehicle and MeHg group in MRM analysis. In general, *p*-values less than 0.01 were taken as statistically significant.

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Table 2. Serum Metabolites with Significant Change in Amounts in the MeHg-Dosed Rats

m/z		chemical formula	fold change[a]	p-value[b]	identified metabolite	KEGG ID[c]	HMDB ID[d]
Positive Ion MS Scanning							
KEGG Pathway: Lysine Biosynthesis (map00300) and Lysine Degradation (map00310)							
277.133	$[M + H]^+$	$C_{11}H_{20}N_2O_6$	0.49	0.0093	saccharopine	C00449	HMDB00279
Negative Ion MS Scanning							
KEGG Pathway: Arachidonic Acid Metabolism (map00590) and Serotonergic Synapse (map04726)							
303.243	$[M - H]^-$	$C_{20}H_{32}O_2$	4.21	0.0043	arachidonic acid	C00219	HMDB01043
315.204	$[M - H]^-$	$C_{20}H_{28}O_3$	3.49	0.0028	15-deoxy-δ-12,14-prostaglandin J2	C14717	HMDB05079
337.247	$[M - H]^-$	$C_{20}H_{34}O_4$	8.26	0.007	11,12-dihydroxy-5Z,8Z,14Z-eicosatrienoic acid	C14774	HMDB02314
335.235	$[M - H]^-$	$C_{20}H_{32}O_4$	7.63	0.0016	leukotriene B4	C02165	HMDB01085
317.199	$[M - H]^-$	$C_{20}H_{30}O_3$	4.17	0.0082	leukotriene A4	C00909	HMDB01337
333.215	$[M - H]^-$	$C_{20}H_{30}O_4$	0.46	0.0066	prostaglandin J2	C05957	HMDB02710
KEGG Pathway: Primary bile Acid Biosynthesis (map00120)							
407.281	$[M - H]^-$	$C_{24}H_{40}O_5$	3.12	0.00007	cholic acid	C00695	HMDB00619
391.302	$[M - H]^-$	$C_{24}H_{40}O_4$	1.74	0.004	chenodeoxycholic acid	C02528	HMDB00518
KEGG Pathway: Dopaminergic Synapse (map04728)							
181.172	$[M - H]^-$	$C_9H_{10}O_4$	2.91	0.00006	homovanillic acid	C05582	HMDB00118

[a]Fold change was calculated by dividing the normalized signal of the metabolite in MeHg group with the normalized signal of the metabolite in the vehicle group. Fold change value greater than one meant the amount of the serum metabolite in the MeHg group was higher than that in the vehicle group. Fold change less than one meant the amount of the serum metabolite in the MeHg group was lower than that in the vehicle group. The signal intensities of all the identified metabolites were normalized with the signal of the internal standard. [b]The p-values were calculated by using a moderated t-test, p-value< 0.01 was considered as significant differences. [c]KEGG ID: Unique C number assigned by KEGG for each metabolite in KEGG database. [d]HMDB ID: Unique identity code assigned by Human Metabolome Database (HMDB) for each metabolite in HMDB database.

RESULTS AND DISCUSSION

Serum PGs and Human Blood THg Levels. Women from Wanshan have significantly higher blood THg levels (mean = 5.47 μg/L) than women from Leishan (mean = 1.47 μg/L) (Table 1). Moreover, serum concentrations of PGF2α, PGE2, and 15-deoxy-PGJ2 of women in Wanshan were also higher (Table 1). Serum concentration of prostacyclin (PGI2) was estimated by quantifying concentrations of its stable metabolic derivatives. However, there was no significant difference between 6-keto-PGF1α and 2,3d-6-keto-PGF1α in the sera of the two groups of women (Table 1). The demographic background and dietary consumption frequencies of the subjects in relation to study sites, blood THg levels, and dietary consumption frequencies have been summarized in Tables S1−S6. Women in Wanshan ate significantly more locally produced rice and local freshwater fishes and poultry, while women in Leishan consumed significantly more aquatic food products and imported freshwater fishes (Table S1). As women in Leishan had significantly lower blood THg levels as well as lower serum concentrations of PGE2, PGF2α, and 15-deoxy-PGJ2; thus, the subjects in the first quartiles of blood THg level and serum concentrations of those 3 PGs shared a dietary habit similar to that of women from Leishan (Table S2 to S6). None of the demographic backgrounds and dietary consumption frequencies was associated with serum PGI2 concentration.

There were significant and strong correlations (R > 0.5) between blood THg levels and serum concentrations of PGE2, PGF2α, and 15-deoxy-PGJ2, but not with PGI2 (Figure 1). The correlations between blood THg levels and serum concentrations of PGs were again found to be strong after adjustments for age, smoking, drinking, and consumptions of aquatic food product and freshwater fish (Table S7). To further investigate the causal relationships between blood THg level, demographic background, dietary consumption frequencies, and serum PG concentrations, partial least squares regression (PLS) was also calculated. Over 50% of the variances (PGE2, log[PGF2α], and log[15deoxy-PGJ2]) can be explained by the first 3 components (Table S8). In general, blood THg levels (>0.8 in first component) and study sites (>0.5 in second component) were predictor variables with the highest loadings in first and second components (Tables S9−S11), explaining around 35−55% of the variances. Consumptions on aquatic food produces, imported freshwater fish, poultry, and other meats were found to be important predictor variables among the second to sixth components (Tables S9−S11), explaining additional 15−20% of the variances. Thus, by PLS regression, blood THg level and study site were the main causes on increases of serum PGE2, PGF2α, and 15-deoxy-PGJ2 concentrations among women in Wanshan and Leishan, followed by dietary habits.

Last, individual DAG graphs had been conducted to understand how potential confounding factors relate to blood THg and prostaglandins (Figures S1−S3). The numerical equations of describing the relationship and the conditional probabilities were provided in the Supporting Information. Results showed that site alone could influence PGE2, PGF2α, and 15-deoxy-PGJ2, and site also influenced blood THg levels. This confirms our PLS results where site explained some of variation in the data set. In addition, site also has influence over a number of variables related to diet. One confounding factor was identified through DAG. For PGF2α, drinking was also found to have influence in addition to site. The drinking habits of mothers in Leishan in our study may therefore also contribute to the change of serum PGF2α concentration. Taken overall, the results of the population study suggest associations between blood THg level and serum PG concentration. It is important to investigate the dose−response relationship using an experimental animal study conducted in controlled environment and serving with constant diets.

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Dysregulations of PG Metabolism in MeHg-Dosed Rats. A controlled rat study was conducted to validate the cause−effect relationship between chronic MeHg expsoure and the alterations in PG metabolism. Serum THg levels of the MeHg-dosed rats reached an average of 65 μg/L of serum at the end of the 12 weeks of MeHg dosing. There was no significant loss in body weight when compared to rats in sham and vehicle group (Figure S4). A nontargeted serum metabolomic study was conducted to investigate metabolic changes induced by the MeHg dosing in the rats using liquid chromatography coupled with a mass spectrometer (LC-MS). Data of both positive ion and negative ion MS scanning were analyzed by principal component analysis (PCA). Serum samples from the vehicle control and MeHg groups (n = 10 in each group) were found to cluster together in the PCA score plot of positive ion MS scanning (Figure S5a). This indicated that most of the positively charged metabolites in the rat serum are nearly the same in both the MeHg-dosing and vehicle control groups. There was one metabolite, saccharopine, that was found to be significantly decreased in the serum of rat after dosing with MeHg (Table 2). Data of serum samples from the MeHg group were clearly differentiated from those from the vehicle group in the PCA score plot of negative ion MS scanning (Figure S5b). This indicated that there were some differential expression of some negatively charged serum metabolites upon MeHg dosing. We found that most of the negatively charged metabolites with a significant increase in amounts were clustered into arachidonic acid metabolism, including arachidonic acid (AA), 15-deoxy-PGJ2, 11,12-dihydroxy-5*Z*,8*Z*,14*Z*-eicosatrienoic acid (11,12-DHET), leukotriene B4 (LTB4), and leukotriene A4 (LTA4) (Table 2). Only prostaglandin J2 (PGJ2) decreased significantly in the rat serum samples after dosing with MeHg. This suggested that the AA metabolism in the rat was altered by bioaccumulation of MeHg. Most importantly, AA metabolism is the main pathway responsible for the synthesis of various types of PGs. Furthermore, amounts of serum cholic acid, chenodeoxycholic acid, and homovanilic acid were found to be significantly increased in MeHg-dosed rats (Table 2). Through pathway analysis of possible serum metabolites that were altered by bioaccumulation of MeHg, we note that PGs were involved in signal transduction in serotonergic postsynaptic neurons (Figure S6). In fact, inorganic mercuric compounds like HgS were known to reduce levels of serotonin 5-HT in brains of mice.[25]

Results of the nontargeted metabolomics study in rats strongly indicated that PGs synthesis of the AA metabolism was altered by chronic exposure to low doses of MeHg. However, the mass spectrometric method adopted by the current metabolomic study was not optimized to detect and quantify all kinds of leukotrienes, prostaglandins, and related metabolites in the rat sera samples. Therefore, ELISA and MRM were performed with the rat sera to quantify amounts of these important metabolites. It was found that serum concentrations of 15-deoxy-PGJ2, PGF2α, and PGI2 in the rat were significantly increased after MeHg dosing (Figure S7a−c), while serum concentrations of TXB2 (a hydrated form of TXA2) and PGE2 showed no significant change (Figure S7d,e). Results from the ELISA assays were consistent with those of serum metabolomic analysis, supporting that prostaglandin and leukotriene metabolism was altered by chronic MeHg exposure. Furthermore, dose−response relationships among levels of MeHg, 15-deoxy-PGJ2, 2,3*d*-6-keto-PGF1α (a stable metabolic derivative of PGI2), and PGF2α were investigated using MRM. Results from MRM revealed that the serum concentrations of 15-deoxy-PGJ2 and 2,3*d*-6-keto-PGF1α started to increase significantly after 6 and 10 weeks of MeHg dosing, respectively (Figure 2a and 2b). However, serum concentration of PGF2α was found to be elevated significantly at the end of the 12 weeks of MeHg dosing (Figure 2c). These observations suggested that the metabolism in producing 15-deoxy-PGJ2 was altered at a lower level of Hg accumulation, followed by alterations of 2,3*d*-6-

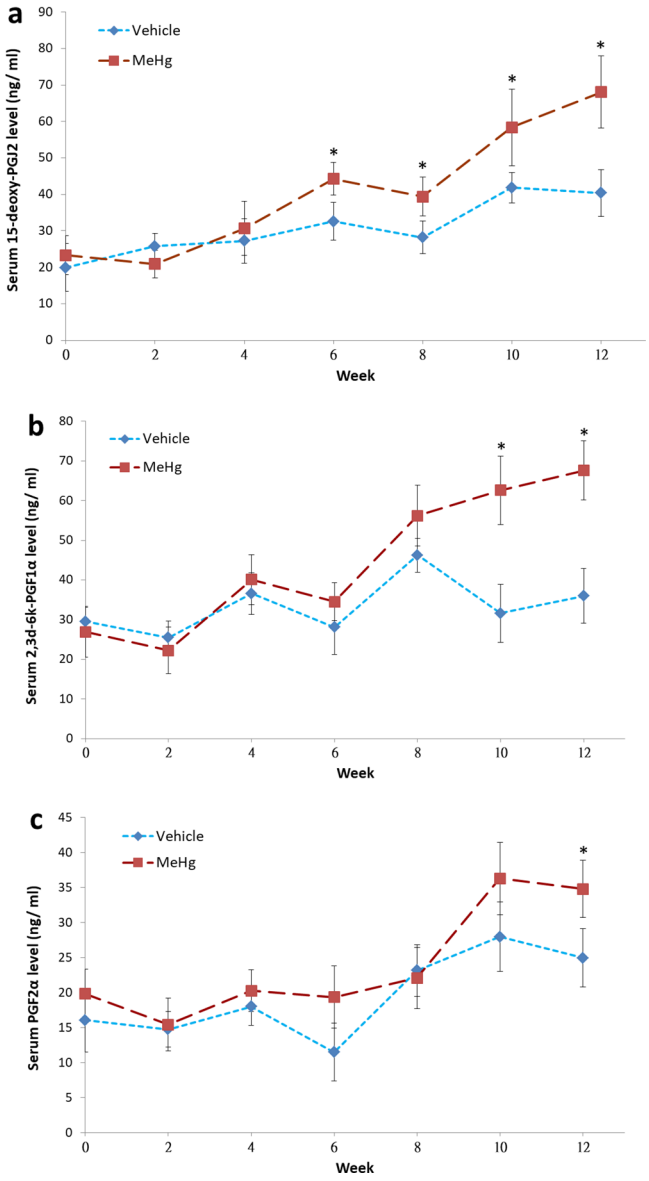

Figure 2. Changes of serum prostaglandins of interest along the 12 weeks of MeHg exposure. Biweekly serum samples were collected from the vehicle and MeHg groups to monitor the changes of (a) 15-deoxy-PGJ2, (b) 2,3*d*-6-keto-PGF1α, and (c) PGF2α. Serum level of 15-deoxy-PGJ2 concentration started to increase significantly (p < 0.05) after 6 weeks of MeHg exposure. Serum levels of 2,3*d*-6-keto-PGF1α started to increase significantly (p < 0.05) after the 10 weeks of MeHg exposure. Serum levels of PGF2 increased significantly (p < 0.05) at 12 weeks in the MeHg-treated rats. The data were presented as mean ± SD.

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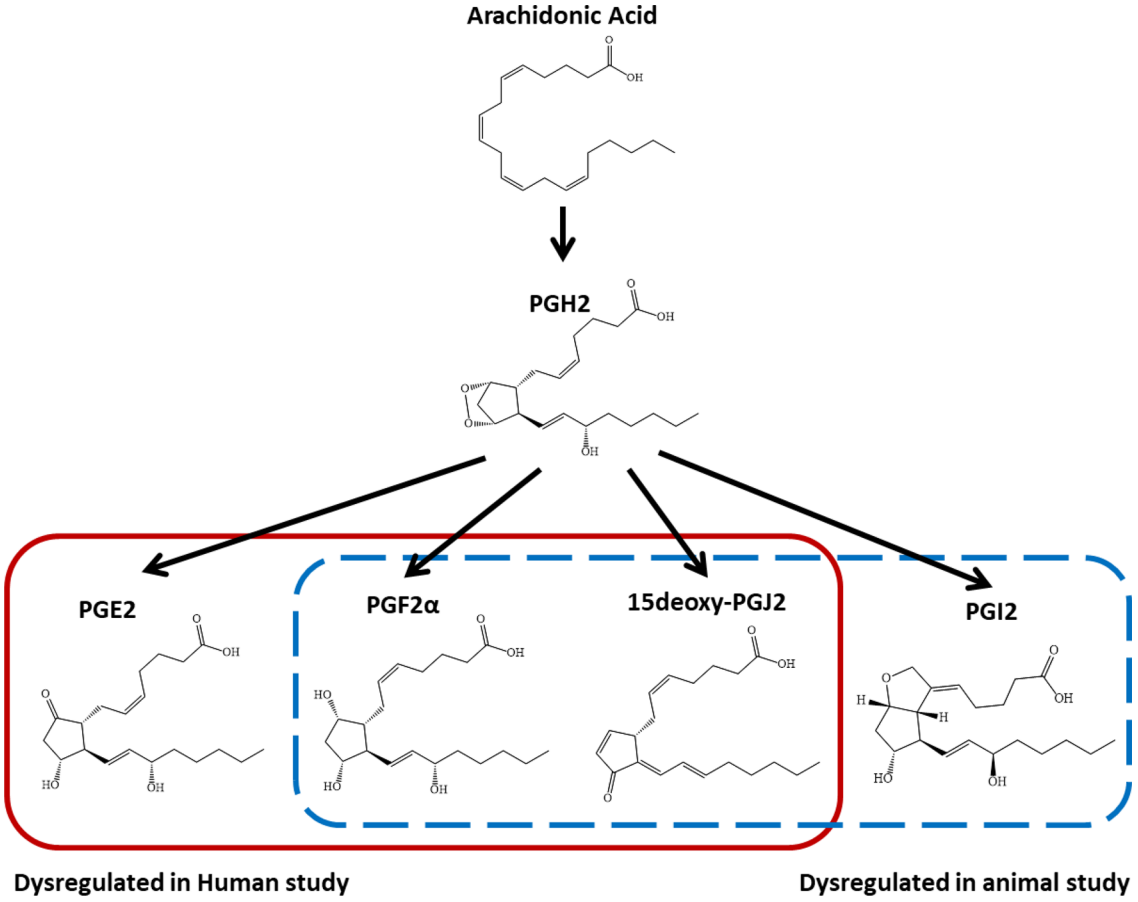

Figure 3. Summary of the current human and animal studies. The above pathway was constructed based on KEGG pathway map of arachidonic acid metabolism (map00590). Arachidonic acid (AA) is the common precursor for PGs. AA is first converted to PGH2 and subsequently converted to PGE2, PGF2α, 15-deoxy-PGJ2, and PGI2 via 4 separate pathways. The patterns of dysregulated PGs have minor difference in between the human and rat studies.

keto-PGF1α and PGF2α metabolisms when THg levels increased further.

Potential Clinical Conditions Associated with PG Dysregulations. This is the first human population study showing a positive association between blood THg and serum PG levels. We have also conducted a rat dosing experiment followed by metabolomics study showing that chronic low dose exposure to MeHg can cause a disruption of AA metabolism resulting in an increase of different PGs. PGF2α and 15-deoxy-PGJ2 were found to increase with blood THg in a dose-dependent manner in both human and rat (Figure 3). In contrast, PGE2 was only found to be positively associated with blood THg in humans, while the increase of PGI2 levels by MeHg dosing was only found in rats. One of possible explanations for the variation observed was due to intrinsic species difference between human and the rats.[26] Others might suggest that the human subjects were pregnant women and the serum samples taken some time before labor. It is known that PGI2 is actively produced by endothelial cells of placental vessels.[27] At the time of labor, concentrations of PGE2, PGF2α, and 2,3*d*-6-keto-PGF1α (a PGI2 stable metabolic derivative) in amniotic fluid would increase significantly.[28,29] In addition, the concentration of PGF2α in maternal blood increases during labor, while the maternal plasma PGE2 level remains nearly constant during pregnancy and parturition.[30] As the PG metabolism changed during pregnancy, so pregnancy may account for the variations in MeHg-induced PG dysregulations seen between human subjects and experimental animals. Nonetheless, it should be stressed that increased levels of PGE2, PGF2α, and 2,3*d*-6-keto-PGF1α were not seen before labor. Our human serum samples were collected 2−3 days before labor. Besides, the rats were kept in controlled environment and with constant dietary intake, while the human subjects in Wanshan and Leishan were exposed to various living environments and obviously had different diets. It is known that PG metabolism was closely associated with diet and lifestyle.[31] This may introduce unknown confounding factors, which may account for the variations on the alterations of PG metabolism between the human subjects and rats.

One of the major biological functions of PGs is to regulate inflammation. PGE2 is a well-known inflammatory mediator that induces fever and cause pain sensation.[32,33] 15-Deoxy-PGJ2 exerts anti-inflammatory property by activating peroxisome proliferator-activated receptor γ (PPARγ), subsequently reducing neuroinflammation as well as a neuronal loss.[34−36] Apart from inflammation, each type of PG plays multiple unique roles in regulating different biological systems. PGF2α was able to induce broncho constriction and uterine contraction.[37,38] PGE2 could induce vasodilation and bronchodilation and regulate motility of gastrointestinal tract.[39−41] PGI2 was a functional antagonist of TXA2. PGI2 was able to induce vasodilation and inhibit platelet aggregation, while TXA2 was able to induce vasoconstriction and activate platelet aggregation.[42−45]

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As elaborated previously, PGs play important regulatory roles in many biological systems and various clinical conditions; hence, dysregulation or abnormal expression levels of PGs could cause hypertension as well as neurodegeneration.[46,47] For example, a high level of 15-deoxy-PGJ2 could induce neuronal apoptosis, and an increase in serum 15-deoxy-PGJ2 concentration was observed in stroke patients.[48,49] The imbalance of PGI2 and TXA2 has an important implication for a diverse range of cardiovascular disease.[50] The increase of serum PGF2α and its isoform 8-iso-PGF2α was associated with myocardial infarction.[51] Increase in serum PGF2α concentration could reduce bile flow and bile acid secretion in the rat model.[52,53] Thus, an increase in serum concentrations in cholic acid and chenodeoxycholic acid in the current part of rat study was suspected to be the result of an increase in serum PGF2α concentration induced by dosing with MeHg (Table 2).

In the literature, there were only a few epidemiological studies that focused on the human immune system upon chronic MeHg exposure.[54]

The results of this cross-sectional study with limited sample size provided evidence for a positive association between chronic MeHg exposure and PG metabolism. A longitudinal cohort study with larger sample size will be needed to investigate the prevalence of clinical abnormalities among residents in Wanshan to confirm the cause−effect relationship that chronic MeHg exposure can induce PG imbalance leading to various clinical abnormalities. This will facilitate a better understanding of the potential health impacts in the populations with frequent consumption of MeHg-contaminated food.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.est.9b00660.

> Materials and methods, demographic backgrounds and dietary consumption, blood THg levels and serum PGs concentrations in human subjects, partial correlations between blood THg and serum concentrations of PGs, variations in blood THg level and serum PG concentrations, directed acyclic graph for PGE2, log[PGF2α], log[15deoxy-PGJ2], principal component analysis score plots, KEGG pathway map, serum prostaglandin concentrations after MeHg treatment, mass transitions for multiple reactions (PDF)

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