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Impacts of Mercury Exposure Levels and Sources on the Demethylation of Methylmercury Through Human Gut Microbiota

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Abstract

This study aims to investigate methylmercury (MeHg) demethylation processes in human gut. Here, we determined the compositions and MeHg demethylation rates of gut microbiota in residents from different Hg exposure levels (Wanshan (WS) town and Yangtou (YT) town) and different Hg exposure sources (Zhuchang (ZC) town and YT town) regions. MeHg and inorganic Hg exposure levels in residents of WS town were significantly higher than those of YT and ZC town. *Desulfovibrio* and *Methanogens,* which related to Hg methylation/demethylation, showed significantly higher abundance in WS and ZC, comparing with YT. In vitro experiments demonstrated that human intestinal microbiota could degrade MeHg directly. Besides, gut microbiota in WS and ZC exhibited significantly higher demethylation rates than YT, suggesting *Desulfovibrio* and *Methanogens* may play important roles in intestinal MeHg demethylation. This study highlights Hg exposure levels and sources may affect demethylation efficiency of gut microbiota, which provides new insights for MeHg demethylation processes in human body.

Keywords Methylmercury · Demethylation · Gut microbiota · Exposure level · Exposure source

Mercury (Hg) is a ubiquitous heavy metal that can be transported over long distances in the atmosphere (Selin 2010) and poses serious health threats to humans and wildlife (Liu et al. 2021). The toxicity of Hg is determined by its chemical form. Methylmercury (MeHg) is a major organic form of Hg and could cause a series of health problems in mammals, such as neurotoxicity, cardiotoxicity, and reproductive toxicity. At present, it is widely reported that exposure to MeHg is caused by ingesting foods with elevated MeHg levels (Cheng et al. 2009). Recent studies have demonstrated that long-term exposure to MeHg is able to decrease the intelligence quotient of children and enhance the probability of cardiovascular disease in adults, which ultimately causing economic losses (Feng et al. 2020).

It has been widely reported that hair is an efficient biomarker of human MeHg exposure. However, Canuel et al. (2006) found the MeHg concentration in hair differed significantly from the amount ingested by the human body. Additionally, bioavailability of MeHg (12%–79%) is lower than the MeHg absorption rate estimated by bio-models (90%–100%) (Bradley et al. 2017). Unknown factors may cause differences between MeHg oral intake and human MeHg burden, which seems to attribute to detoxification/elimination of MeHg in human body. With the development of biomolecular technologies, the factors/mechanisms of toxic environmental pollutant degradation by intestinal microorganisms have received more attention (Liu et al. 2019). Previous works reported that gut microbiota in humans could enhance the degradation of polycyclic

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aromatic hydrocarbons (PAHs) and Polychlorinated biphenyls (PCBs) (Claus et al. 2016; Van et al. 2005). In addition, some studies also have demonstrated that intestinal microorganisms in human, marine fish and mice can promote the demethylation of MeHg (Li et al. 2019). High Hg exposures are considered posing hazardous to gut microbiota, which eventually reduced or changed the abundance of microbiota in mice gut (Liu et al. 2019). However, the impacts of Hg exposure levels on demethylation of human gut are still unclear. On the other hand, it is widely accepted that fish and rice consumption are the major pathways of human MeHg exposure (Cheng et al. 2009). Dose–response relationship of MeHg in population with rice consumption was confirmed to be different with that in population relying on fish consumption (Li et al. 2015). This result suggests that different types of food Hg sources may influence the demethylation rate of intestinal microbiota. However, this hypothesized also have never been demonstrated.

In this study, people living in WS Town (high Hg exposure through rice consumption), Zhuchang (ZC) Town (low Hg exposure through fish consumption) and Yangtou (YT) Town (low Hg exposure through rice consumption) of Guizhou Province were selected. We analyzed compositions and MeHg demethylation rates of gut microbiota in selected people exposed to different MeHg levels (WS and YT) and different MeHg sources (YT and ZC). This research aims to study the interaction between MeHg levels/sources and intestinal microbiota, and to better understand MeHg detoxification processes in human body.

Materials and Methods

The sites of WS Town of Tongren City, YT Town of Tongren City, and ZC Town of Guiyang City in Guizhou Province are shown in Fig. 1. Early studies have demonstrated that rice grown around WS Hg mine in Guizhou Province has a very strong capacity for MeHg accumulation, resulting in a high-rice-Hg exposure to local people (Zhang et al. 2010). ZC town is located in Guiyang city, and Du et al. (2018) used Hg stable isotope identified that human MeHg burden via fish consumption in Guiyang is higher than in other areas of Guizhou. In addition, ZC town is close to Baihua Reservoir in Guiyang, which represented an area with frequent consumption of fish for local residents. Because fish Hg concentrations in the market of Guiyang are generally low, ZC could be considered as low-fish-Hg exposure region. YT is distant from Hg pollution region and people lived in YT town rarely consumed fish; therefore, YT is considered as a low-rice-Hg exposure area in this study.

Based on a questionnaire survey, we selected healthy residents of WS and YT who frequently consumed rice (> 14 times per week) but rarely consume fish (< 2 meals per year), and healthy residents of ZC who frequently consumed fish (> 1 meal per week). We excluded residents with these criterions: (1). pre-existing gastrointestinal disease; (2). use of antibiotics in the past 6 months; (3). consumption of any foods or supplements containing probiotics in the past month. Moreover, the three groups have similar gender ratios and showed no statistically significant difference in age, height or body weight (Table 1). All participants signed informed consent forms. The project was approved by the Ethics Committee for human experiments at Guizhou Medical University (approval no. 2020–75). A total of 33 hair, 33 urine and 33 faeces samples were collected from volunteers in WS (n = 11), YT (n = 11) and ZC (n = 11). In lab, total Hg (THg) levels in hair and faeces samples were measured using a Milestone Direct Mercury Analyzer 80 (DMA-80; Italy). THg concentrations in urine were measured by the acid digestion and Cold Vapour Atomic Fluorescence (CVAFS) method. The MeHg in hair samples was digested by 5 mL 25% KOH solution (m/m). Faeces samples were digested by 5 mL 25% KOH solution (m/m) and extracted by the organic phase with CH_2Cl_2 solution. Hair and faeces digested solution were detected by ethylation and gas chromatography CVAFS (GC-CVAFS) method (Tekran 2700) (Grajewska et al. 2020).

Frozen stool samples (− 80°C) were shipped to Shanghai Majorbio Bio-pharm Technology Co., Ltd for microbiome research. A total of 200 mg of faeces samples were collected and the total DNA were extracted using the PowerSoil DNA extraction kit. The operational steps were conducted according to the specifications of the kit. Bioinformatics analysis was carried out after obtaining the original data and the data were analyzed on the online platform of Majorbio Cloud Platform. Subsequently, metagenomic sequencing was performed using the Illumina Hiseq Xten sequencing platform. Reads were compared with host DNA sequences by software BWA and contaminated reads with high similarity were removed. MEGAHIT was used to assemble the optimized sequences and contigs larger than 300 bp were screened as the final assembly results. A genomic sequence database of Mer operons was established through KEGG Database (Kyoto Encyclopedia of Genes and Genomes) (Kanehisa et al. 2014). This study searched for Hg resistance gene (Mer operon) and Hg methylation gene (hgcAB) in faeces samples of 33 residents after KEGG functional annotation of metagenomic sequencing.

MeHg degradation experiment was conducted under an anaerobic condition in 37°C to reflect the gut environment. The procedures were as followed: about 1 g of faeces sample (wet weight) was collected. A filter sterilized solution of Phosphate buffer saline (PBS) was added into a 50 mL centrifuge tube with solid faeces: liquid ratio of 1:10 and shaken evenly. After filtering with sterile medical gauze to remove larger fecal debris, 100 µL faeces solution was added into

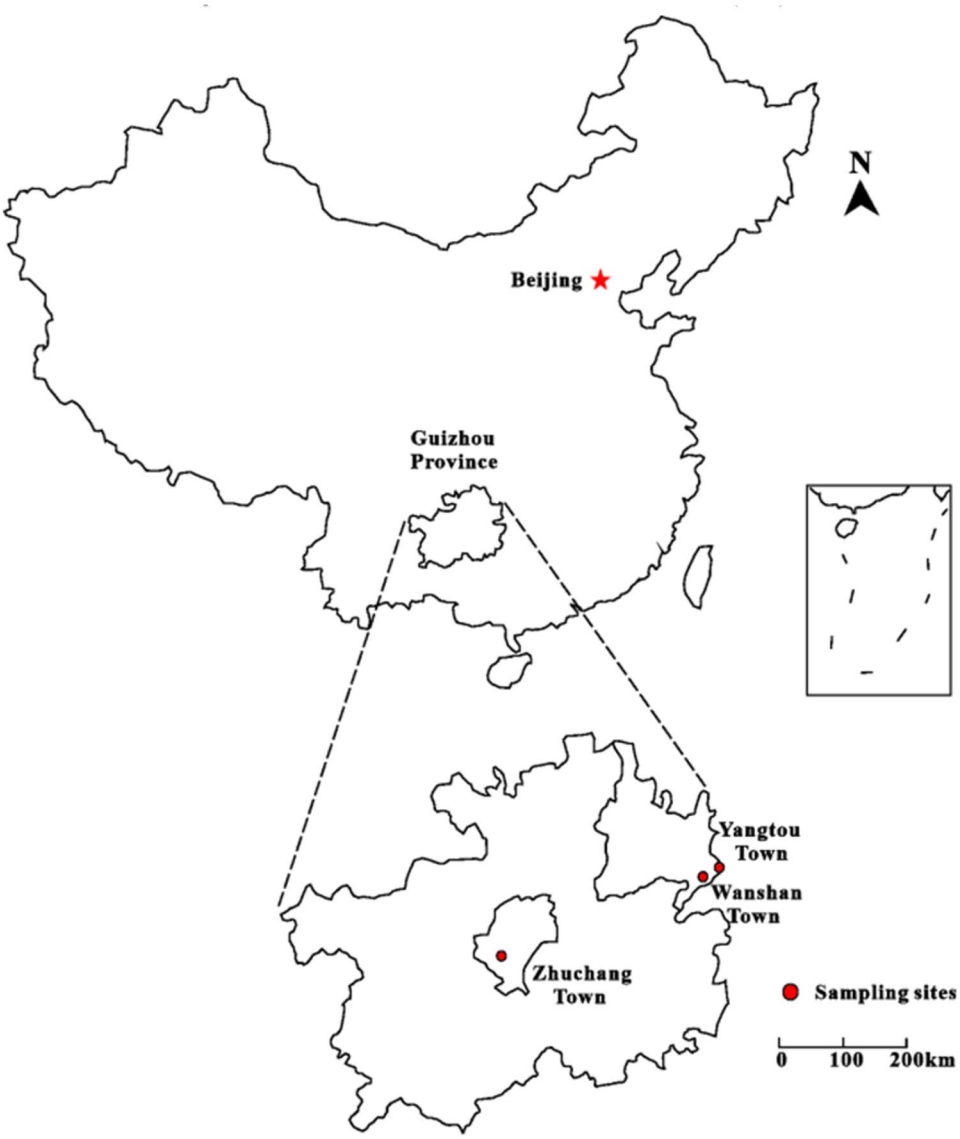

Fig. 1 Spatial distributions of the study sites

Table 1 Basic information of the study population in three sites

Site	n	Male	Female	Age(year)	Height(cm)	Weight(kg)
WS	11	4	7	44.2 ± 9.62	158.8 ± 8.49	60.9 ± 12.7
YT	11	5	6	42.8 ± 8.64	159.8 ± 6.51	60.4 ± 7.57
ZC	11	5	6	37.7 ± 11.2	158.7 ± 5.37	56.0 ± 6.69

10 mL Luria–Bertani medium. MeHg standard solution was added to the inoculated medium (samples were wrapped and kept in darkness during culturing) to create MeHg concentrations of 1.5 nM, which is similar with fecal background value (Liu et al. 2022). Control group (no microbiota added) and sterilized group were also added to avoid the abiotic effect. The MeHg concentration in the cultured solution was tested at different time points (0 h, 6 h, 12 h, 24 h, 36 h and 48 h), which aimed to determine the net content of MeHg degradation in different periods. The MeHg degradation rate was calculated as the ratio of eliminated fraction of MeHg (%) and degradation time period. Two replicate samples were used for each presentment during the MeHg degradation experiment.

Blanks, certified reference materials (CRMs), and duplicate analysis were used for quality control of the experimental process. The limits of determination (LOD) for THg and MeHg were 0.02 and 0.003 μg/kg, respectively. The relative standard deviations of duplicate analysis were < 10% and the recovery of the CRMs ranged from 91.8% to 105%

(Table S1). Quantitative data are presented as means ± standard deviation (SD). Results were considered statistically significant if $p < 0.05$.

Results and Discussion

THg and MeHg concentration in hair and urine of the three sites are listed in Table 2. The hair THg in WS, YT and ZC residents varied from 0.884–5.84 mg/kg, 0.253–1.49 mg/kg and 0.0680–0.796 mg/kg, respectively; while hair MeHg ranged from 0.776–3.92 mg/kg, 0.106–1.12 mg/kg and 0.068–0.413 mg/kg, respectively. The averaged hair Hg and MeHg levels in WS exceeded the safe limit (1 mg/kg, USEPA, 1997). Similarly, the urine THg levels in the WS Group (1.66 ± 0.851 μg/L) were also significantly higher than those of the YT (0.575 ± 0.615 μg/L) and ZC Groups (0.409 ± 0.353 μg/L). These results overall indicated high MeHg and IHg exposure in WS. Human MeHg exposure in WS may mainly derived from rice consumption (Zhang et al. 2010). Given the high Hg concentration in soil, atmosphere and water bodies of WS, local people also indicated relatively high IHg ingestion dose. Moreover, a recent study used Hg isotopes confirming a fraction of IHg in urine might be from demethylation of MeHg in human body (Du et al. 2021). Hence, it is speculated that the high urine THg content in the WS Group may also relate to high exposure to MeHg (Du et al. 2021).

For microbiota α diversity analysis, microbial richness (Chao1 and ACE indices) and microbial diversity (Shannon and Simpson indices) indicated no significant difference in YT versus WS ($p > 0.05$) and YT versus ZC ($p > 0.05$). It is suggested that the growth of intestinal microbiota may not be impacted by Hg exposure levels or Hg exposure sources (Table S2). However, the PCoA analysis of β diversity results showed significant differences in the microbial community composition among YT versus WS ($R = 0.29$; $p = 0.026$) and YT versus ZC ($R = 0.28$; $p = 0.024$) (Fig. 2). Histograms of relative phylum abundance of human intestinal microbiota from three sites were shown in Fig. 3. The abundance of microbiota in class levels are given in Figure S1. Overall, Firmicutes, Bacteroidetes, Proteobacteria, Actinobacteria and Fusobacteria were the predominant phyla (accounted for > 95%) in the gut of humans.

Intestine of high-Hg exposed people showed comparable abundance of Firmicutes, Bacteroidetes, Actinobacteria

Table 2 THg, MeHg levels, and MeHg ratio in biomarker samples from three sites

	Unit	WS (n = 11)	YT (n = 11)	ZC (n = 11)
Hair THg	mg/kg	2.19 ± 1.62	0.614 ± 0.403	0.334 ± 0.225
Hair MeHg	mg/kg	1.68 ± 0.964	0.390 ± 0.324	0.205 ± 0.120
Hair MeHg/THg	%	83.2 ± 14.8	59.3 ± 17.2	70.8 ± 22.9
Urine THg	μg/L	1.66 ± 0.851	0.575 ± 0.615	0.409 ± 0.353
Faeces THg	mg/kg	0.553 ± 0.368	0.0900 ± 0.0826	0.0470 ± 0.0180
Faeces MeHg	μg/kg	0.519 ± 0.335	0.201 ± 0.211	0.123 ± 0.0780
Faeces MeHg/THg	%	0.135 ± 0.119	0.386 ± 0.496	0.319 ± 0.220

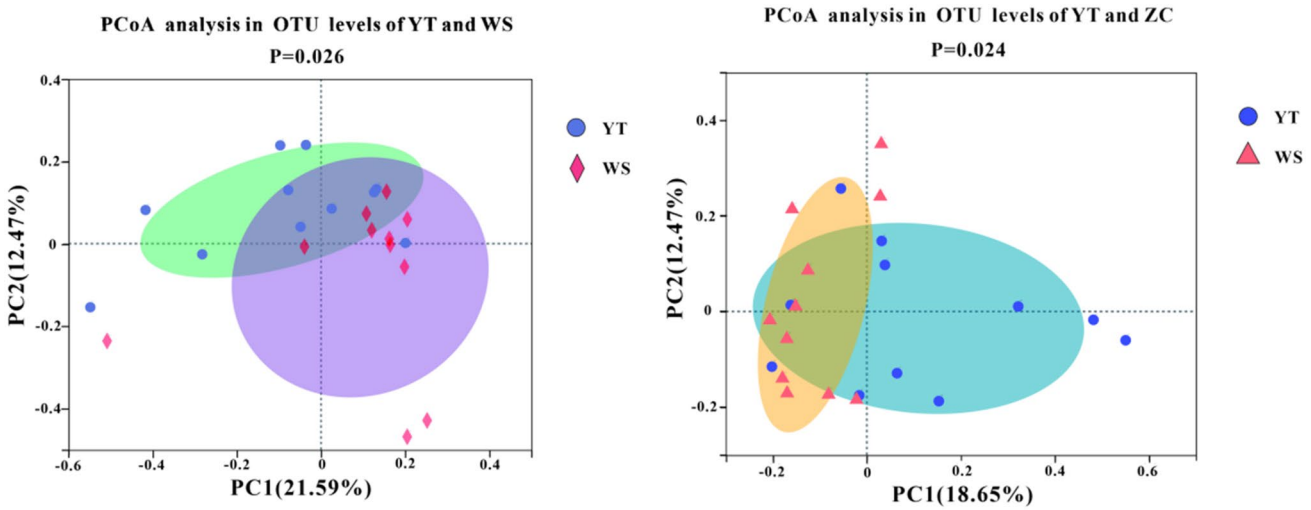

Fig. 2 Principal coordinates analysis (PCoA) results of gut microbial communities from YT versus WS (**A**) and YT versus ZC (**B**)

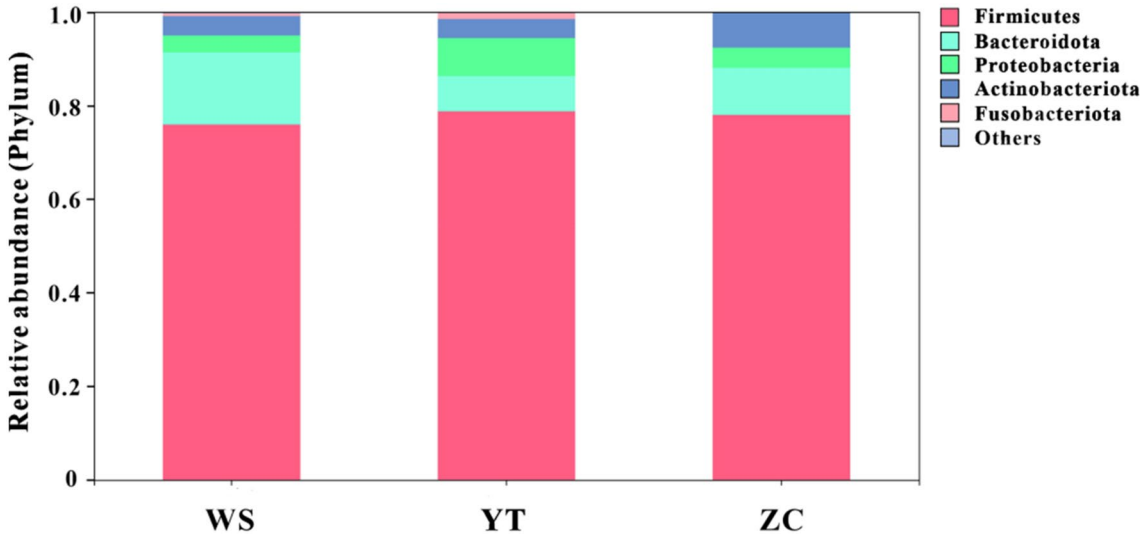

Fig. 3 Relative abundance (phylum level) of gut microbiota from WS, YT and ZC

and Fusobacteria, compared to low-Hg exposed people ($p > 0.05$), by the Wilcoxon rank-sum test. However, significant ($p = 0.026$) higher abundances of Proteobacteria were observed in YT (8.12% on average) than those in WS (3.62% on average) (Fig. 3; Fig. 4A). Within Proteobacteria phyla, significant lower ($p = 0.026$) abundances were observed in Gammaproteobacteria class in WS gut microbiota compared with YT (Figure S1). Nielsen et al. (2018) have reported Gammaproteobacteria related to trans-sulfuration metabolism may sensitive to MeHg exposure, besides, Yang et al. (2021) also found a significant decreasing of the community abundance of Gammaproteobacteria in marine fish exposed to high MeHg levels (*Acanthopagrus latus*). This suggests high Hg exposure in WS population have affected the relative abundance of Hg sensitive microbiota. In addition, microbiota related to Hg methylation/demethylation such as *Desulfovibrio* and *Methanogens* (*Methanothrix sp. and Methanosarcinales sp.*) (Barkay and Gu 2022) were significantly higher ($p < 0.05$) in WS, compared to those in YT (Table S3). *Desulfovibrio* and *Methanogens* are not dominant species in human gut (relative abundance < 0.2%), but played important roles in Hg transformation in the environment (Barkay and Gu 2022). It seems that Hg exposure should reduce the relative abundance of gut microbiota which may influence immunomodulation, antimicrobial properties, and intestinal barrier fortification (Liu et al. 2019). However, Nielsen et al. (2018) found that fish intestinal microbiota may change the community composition as an adaptive response to increase MeHg detoxification. Several genus abundances (e.g., *Xanthomonadaceae*) were observed significantly increased in heavy metals' removal or xenobiotic metabolism in fish gut, when exposed to dietary MeHg. *Desulfovibrio* and *Methanogens* could remove MeHg in anaerobic conditions. Therefore, higher *Desulfovibrio* and *Methanogens* abundance in gut of WS people may attribute to the intestinal MeHg detoxification.

The relative abundance of Firmicutes, Bacteroidetes, Proteobacteria and Fusobacteria in different regions are comparable ($p > 0.05$) (Fig. 3; Fig. 4B). While gut microbiota in ZC exhibited significant higher ($p = 0.042$) abundance of Actinobacteria (7.49% on average) compared with those in YT (4.07% on average) (Fig. 3; Fig. 4B). The abundances of *Desulfovibrio* and *Methanogens* in gut exposed to fish-Hg were significantly higher ($p < 0.05$) than those in rice-Hg exposure (Table S3). Different Hg exposure sources represents the different dietary habits of individuals. The MeHg exposure via fish consumption may somewhat enhance the ingestion of nutrition (e.g., protein or omega 3). By contrast, MeHg exposure via rice consumption may result in less protein and more carbohydrate intake. Because consumption of carbohydrate or protein is able to change the microbiota community structure (Guo et al. 2018), high abundance of those gut microbiota in ZC might be caused by dietary structure with high nutrition intake. As a result, we proposed that different Hg exposure levels and sources could affect the composition of typical bacterial community (especially for *Desulfovibrio* and *Methanogens*) of intestinal microbiota.

The THg concentrations in the faeces of the WS, YT and ZC Groups ranged from 0.153–1.34 mg/kg, 0.0307–0.323 mg/kg and 0.0246–0.0924 mg/kg, respectively. MeHg levels in faeces ranged from 0.0800–1.14 μg/kg, 0.0200–0.760 μg/kg and 0.0100–0.260 μg/kg, respectively (Table 2). The proportions of MeHg/THg in faeces samples only averaged at 0.135% ± 0.119%, 0.386% ± 0.496% and 0.319% ± 0.220%, respectively. This is consistent with the extremely low proportions of MeHg

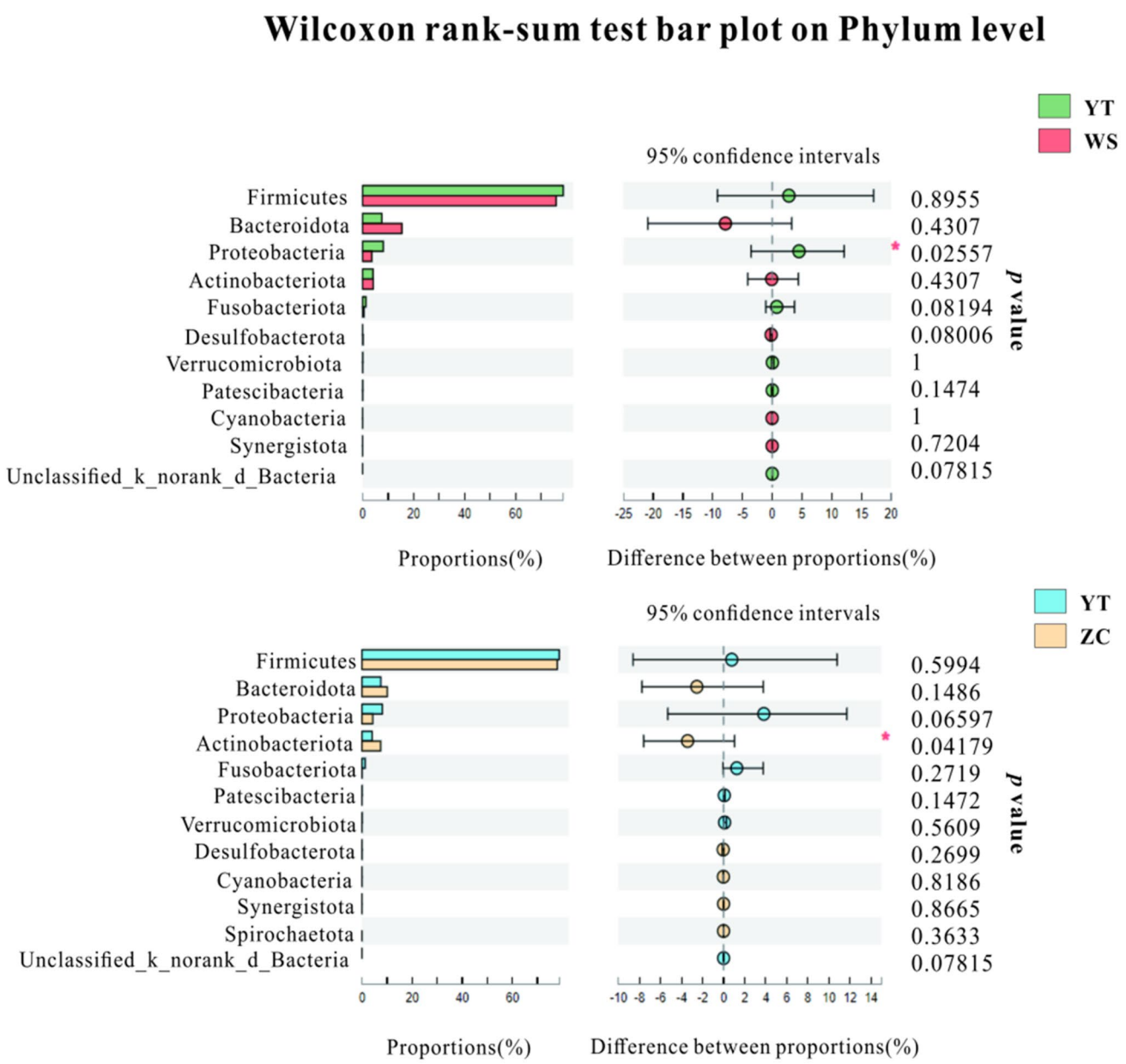

Fig. 4 Gut microbiota abundance comparison (phylum level) of YT versus WS (**A**) and YT versus ZC (**B**)

in human faeces (0.0058%–5.8%, n = 17) reported by previous study (Rothenberg et al. 2016). The low proportion of MeHg in fecal samples may attribute to the biokinetic fact that MeHg is hardly been eliminated comparing with Hg(II) (Clarkson 2002).

In vitro demethylation experiments found that the MeHg concentration in the control group and sterilized group changed slightly under the 1.5 nM MeHg levels. While MeHg concentration in media added with gut microbiota decreased significantly (Fig. 5). This result indicated that gut microbiota from these three sites have the potential to demethylate MeHg directly. The demethylation rates of gut microbiota were shown in Fig. 5. Overall, 62%, 43% and 68% of MeHg were degraded during 0-6 h in WS, YT and ZC, respectively. At 48 h, 89%, 76% and 81% of MeHg were degraded in WS, YT and ZC, respectively. The MeHg demethylation rates in 0–6 h (WS: 10.4% h^{-1}; YT: 7.1% h^{-1}; ZC: 11.4% h^{-1}) were significantly higher ($p < 0.05$) than those in 6-48 h (WS: 1.7% h^{-1}; YT: 1.4% h^{-1}; ZC: 1.0% h^{-1}) from three regions. Within 0–6 h, the gut microbiota of ZC and WS groups exhibited comparable demethylation potential ($p > 0.05$). YT group displayed significantly lower demethylation rate ($p < 0.05$) compared to ZC and WS groups. Although three regions showed no significant difference of

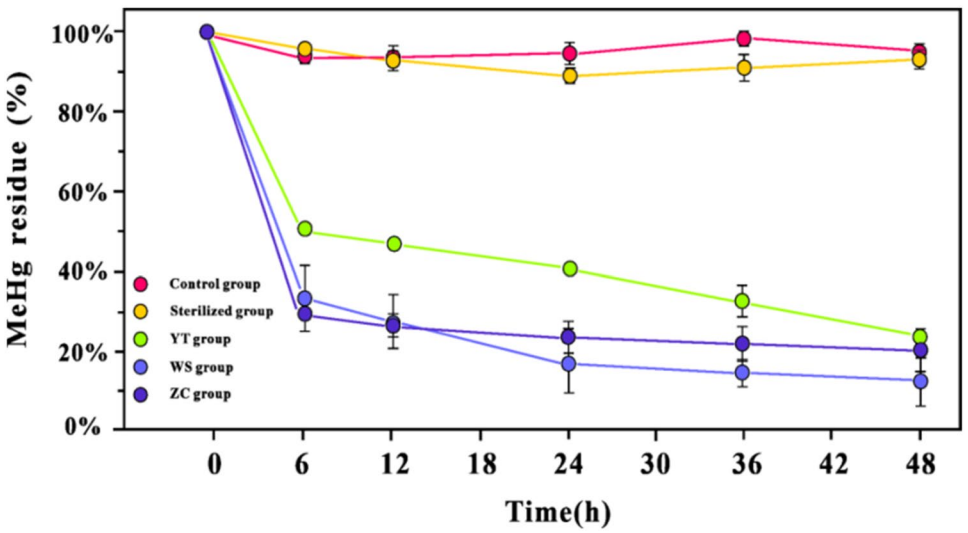

Fig. 5 MeHg demethylation efficiency of gut microbiota form three sites. The X axis represents the reaction time (h), and the Y axis represents the MeHg residue (%)

MeHg demethylation rate during 0-48 h, we suspected that most of MeHg (> 80%) were degraded in 48 h and finally exhibited approximate demethylation rates in three regions. Reductive demethylation and oxidative demethylation were considered as the two predominate ways for MeHg demethylation in the environment. Reductive demethylation is considered as the major demethylation way in fish or mice gut (Li et al. 2019; Rowland et al. 1978). Yang et al. (2021) detected significant increasing of merA operon in fish gut when exposed to high dietary MeHg. However, this study observed extremely low abundance of mer operon in human gut (Table S4), which is consistent with previous study (Guo et al. 2018). It is suggested that reductive demethylation may not be the predominate way of MeHg demethylation in human gut (Guo et al. 2018; Rothenberg et al. 2016). According to Sect. 3.2, we found *Desulfovibrio* and *Methanogens* abundance in WS and ZC human gut are significantly higher than those in YT (Table S3). Although these two strains were widely reported as Hg methylator (Barkay and Gu 2022; Guo et al. 2018), which depended on hgcAB genes. This study has not found hgcAB genes in feces samples (as shown in Table S4), suggesting the Desulfovidrio and Methanogens in human gut could not methylate Hg. While these two microbiotas have been also considered as major players in oxidative demethylation (Li et al. 2019). MeHg could be degraded under strict anaerobic conditions with pure cultures of the *Methanogen* (*Methanococcus maripaludis*) and *Desulfovibrio* (*desulfuricans*) (Pak and Bartha 1998). The mechanism of oxidative demethylation may attribute to one-carbon (C1) metabolism of *Desulfovibrio* and *Methanogens*. MeHg likely act as electron donor for the reactions (Barkay and Gu, 2022). Recent study also confirmed that *Desulfovibrio* could produce H_2S. Subsequently, H_2S could react with MeHg to $(CH_3Hg)_2S$ intermediates (Jonsson et al. 2016). Even the mechanism of MeHg degradation is still unclear, these two microbiotas could certainly affect the ability of MeHg demethylation. Higher relative abundance of *Desulfovibrio* and *Methanogens* in gut are expected to explain higher MeHg demethylation rates in WS and ZC.

In conclusion, WS residents have higher MeHg and IHg exposure risks compared to residents of YT and ZC. Hg exposure levels and dietary structure may affect the composition of human gut microbiota. WS and ZC groups exhibited higher abundance of *Desulfovibrio* and *Methanogens* compared with those in YT group. Additionally, gut microbiota in WS and ZC groups also presented relatively higher MeHg demethylation rates compared to those in YT. Our observation primarily proposed that *Desulfovibrio* and *Methanogens* may play important roles in human MeHg demethylation without controlling by mer operons. However, the detailed abiotic/biotic mechanisms of MeHg demethylation in human intestinal environment are still needed to be investigated. Additional work needs to isolate intestinal *Desulfovibrio* and *Methanogens* strains to study the detailed mechanisms of gut microbiota MeHg demethylation.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00128-022-03569-5.

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