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# The association of carotid intima-media thickness with serum Level of perfluorinated chemicals and endothelium-platelet microparticles in adolescents and young adults

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ABSTRACT

Perfluorinated chemicals (PFCs) have been widely used in a variety of products worldwide. Our previous study has documented a close association of higher serum level of perfluorooctane sulfonate (PFOS) with an increased carotid intima-media thickness (CIMT) in a cohort of adolescents and young adults. Herein, we further investigated the association of oxidative stress, circulating endothelial microparticles (EMPs) and platelet microparticles (PMPs) with PFCs and CIMT in humans. We recruited 848 subjects (12–30 years old) from a population-based sample to determine the relationship between serum levels of PFCs, EMPs (CD62E and CD31+/CD42a−), PMPs (CD62P and CD31+/CD42a+), and the urine levels of 8-hydroxydeoxyguanosine (8-OHdG) and CIMT. The results showed that CD31+/CD42a− (endothelial apoptosis marker) and CD31+/CD42a+ (platelet apoptosis marker) increased significantly across quartiles of PFOS in multiple linear regression analysis. Furthermore, the elevation of CD31+/CD42a− and CD31+/CD42a+ corresponded to the increase of the odds ratios of thicker CIMT (greater than 50th percentile) with higher serum PFOS concentration (greater than 50%) (OR = 2.86, 95% C.I. = 1.69–4.84, $P < 0.001$) in logistic regression models. There was no association between PFC concentration and 8-OHdG. In conclusion, we found the positive association between PFOS and CIMT that was more evident when serum levels of EMPs (CD31+/CD42a−) and PMPs (CD31+/CD42a+) were elevated. Further studies are warranted to investigate the causal inference of PFOS exposure on endothelial cell damage and atherosclerosis.

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## 1. Introduction

Perfluorinated chemicals (PFCs) are a class of highly stable man-made compounds composed of a variable length of fluorinated carbon backbone and a carboxylate or sulfonate functional group. They have been used in industrial and consumer products, such as surface treatments for carpets and fabrics, food packaging, and fire-fighting foam (Houde et al., 2006). The two most widely known PFCs are perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS), which belong to the 8-carbon backbone subgroup. In Taiwan, PFCs (especially PFOS) are used during the photo-lithotripsy process in semi-conductive industry and have severely contaminated the downstream rivers and aquatic ecosystems (Lin et al., 2009a, 2010). Moreover, a higher concentration of perfluorodecanoic acid

*Abbreviations:* 8-OHdG, 8-hydroxydeoxyguanosine; BMI, body mass index; CIMT, carotid intima-media thickness; SBP and DBP, systolic and diastolic blood pressure; EMPs, endothelial microparticles; hs-CRP, high sensitivity C-reactive protein; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HOMA, homeostasis model assessment of insulin resistance; NHANES, National Health and Nutrition Examination Survey; NTD, new Taiwan dollar; PFCs, perfluorinated chemicals; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonate; PFNA, perfluorononanoic acid; PFUA, perfluoroundecanoic acid; PMPs, platelet microparticles; RANTES, regulated on activation, normal T cells expressed and secreted.

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(PFUA) (Lien et al., 2011; Lin et al., 2013b) had been reported than other biomonitoring literature in U.S. (Calafat et al., 2007). The public health relevance of PFCs exposure is still undefined because the adverse health effects resulting from chronic and low-level exposure of PFCs have not been adequately studied (Lau et al., 2007).

Dietary exposure has been suggested as the main exposure route of PFCs in general populations (Haug et al., 2010). After exposure, PFCs are weakly lipophilic, very water soluble, and bind preferentially to proteins. Approximately 90% to 99% of the PFCs in the blood are bound to serum albumin. PFCs are primarily extracellular and accumulate primarily in the liver, blood serum, and kidneys (Lau et al., 2007). The half-life of serum elimination of PFCs in humans appears to be years. The longer the carbon chain length, the longer PFCs persists in the body. For example, the geometric mean half-lives of serum elimination of perfluorobutane sulfonate (a 4-carbon PFC), on average, in a little over one month in humans, while PFOA and PFOS are 3.5 (95% CI, 3.0–4.1) and 4.8 (95% CI, 4.0–5.8) years, respectively (Olsen et al., 2009). However, perfluorohexane sulfonic acid, a 6-carbon compound, is an exception to the rule as it is eliminated in 7.3 years of half-lives (95% CI, 5.8–9.2) (Olsen et al., 2007).

Recently, several epidemiological studies have suggested an association between PFC exposure and cardiovascular risk factors. Exposure to PFOA and PFOS is associated with increased total cholesterol and low-density lipoprotein cholesterol (LDL-C) (Frisbee et al., 2010; Nelson et al., 2010; Steenland et al., 2009) and increased uric acid levels (Steenland et al., 2010). Moreover, higher serum PFOA levels are associated with high homocysteine levels and hypertension (Min et al., 2012), and PFOS is also associated with insulin resistance (Lin et al., 2009b). In a representative sample, based on the National Health and Nutrition Examination Survey (NHANES), higher serum PFOA concentrations are associated with self-reported cardiovascular disease and peripheral arterial disease (Shankar et al., 2012). Recently, we found that carotid intima-media thickness (CIMT) is increased significantly across quartiles of PFOS after adjustment for traditional cardiovascular confounders (Lin et al., 2013b), suggesting that PFCs are associated with atherosclerosis.

Given that PFOA and PFOS have been associated with hypertension, atherosclerosis and cardiovascular disease, it is interesting to investigate whether exposure to PFOA and PFOS can induce vascular endothelial dysfunction, the critical risk in the development of atherosclerosis and cardiovascular disease. In vitro studies have shown that PFOS and PFOA exposure can cause increase oxidative stress (Hu and Hu, 2009; Liao et al., 2012), induce actin filament remodeling, change endothelial permeability (Qian et al., 2010), increase leukocyte cell membrane fluidity and mitochondrial membrane potential (Hu et al., 2003), trigger the opening of tight junctions (Wang et al., 2011b), and promote inflammation and overexpression of endothelial cell-adhesion molecules (Liao et al., 2012). However, the clinical information on the relationship between PFCs and oxidative stress, vascular endothelial damage, and CIMT has not been defined.

Microparticles are defined as small (100–1000 nm) lipid bilayer limited vesicular bodies originating from activated or apoptotic cells, which contribute to endothelial dysfunction and the development of cardiovascular diseases. Microparticles may trigger endothelial dysfunction by disrupting production of nitric oxide release from vascular endothelial cells and subsequently modifying vascular tone. In addition, microparticles can promote coagulation and inflammation or alter angiogenesis and apoptosis in endothelial cells (Lovren and Verma, 2013). Endothelial microparticles (EMPs) and platelet microparticles (PMPs) are used as biomarkers of vascular endothelial dysfunction because the level of these vesicles is a sensitive indicator of the nature and extent of endothelial injury in cardiovascular diseases (Werner et al., 2006). Several different markers are used to identify EMPs and PMPs, and each marker has different clinical implications. Apoptotic endothelial cells shed EMPs in which constitutive markers such as CD31+/CD42a− predominate (Dignat-George and Boulanger, 2011), whereas CD31+/CD42a+ is defined as a PMP marker shed from apoptotic platelets (Chirinos et al., 2005a; Gonzalez-Quintero et al., 2003). Activated endothelial cells shed EMPs in which inducible markers such as CD62E (Lee et al., 2012).Moreover, previous studies have shown that patients with cardiovascular diseases have an excess of circulating CD62P PMP, which is a sensitive measure of platelet activation (Ault et al., 1999; Marquardt et al., 2002). As to health effects of environmental exposure to endocrine disrupting chemicals, we have demonstrated a higher MEHP concentration in urine was associated with an increase in endothelial and platelet microparticles in the YOung TAiwanese Cohort (YOTA) study (Lin et al., 2016).

Herein, we designed a cross-sectional study in adolescents and young Taiwanese adults based on a nationwide mass urine screening. In the current study, we used CIMT as a surrogate marker of atherosclerosis and the urinary oxidized nucleoside 8-hydroxydeoxyguanosine (8-OHdG) as a surrogate marker of oxidative stress because this substance has been widely used as an index of cellular oxidative stress (Wu et al., 2004). We also used EMPs and PMPs as biomarkers of vascular endothelial dysfunction. The goal of this study was to assess the association between serum levels of PFCs, EMPs (CD62E, CD31+/CD42a−), and PMPs (CD62P, CD31+/CD42a+), as well as urinary level of 8-OHdG and the CIMT in the YOTA study.

## 2. Materials and methods

### 2.1. Study population and data collection

The study population, the YOTA cohort, was composed of students who participated in the 1992–2000 mass urine-screening program in Taiwan (Wei et al., 2003). Detailed information on the study subjects has been published before (Lin et al., 2013b). In our previous study, we only measure serum PFCs in 644 of all 790 subjects because of the limited availability of serum samples (Lin et al., 2013b). In the present study, we further joined 97 best friend control group and a total 886 subjects were included in this study [10, 25–26]. The subjects were interviewed and given cardiovascular health check-ups at the National Taiwan University Hospital (NTUH) between 2006 and 2008. The study was approved by the Research Ethics Committee, NTUH. Written informed consent was obtained from each participant or from the parents of children and adolescents when they enrolled in the follow-up study. A detailed flow chart of the selection process is shown in Fig. 1. Because of the limited availability of serum samples, individuals without serum tests for PFCs (N = 38) and EMPs, PMPs (N = 1) were excluded. A total of 848 participants were included in the final analysis.

### 2.2. Anthropometric and biochemical data

Socio-demographic information, such as age, gender, history of medication, and household income, was recorded during the interview. The extent of alcohol intake was determined by questionnaire and was categorized into two groups – “current alcohol consumption” and “no alcohol consumption now.” Smoking status was categorized as “active smoker,” “passive smoker,” or “has never smoked.” Household income was categorized as either “above 50,000 new Taiwan dollars (NTD) per month” or “below 50,000 NTD.” Body mass index (BMI) was calculated as body weight (in kg) divided by the square of body height (in meters). Two seated blood pressure and heart rate measurements were obtained at least one minute apart after five minutes of rest by using a mercury manometer and the appropriate cuff size.

Serum levels of cholesterol, triglycerides, low density lipoprotein cholesterol (LDL-C), and glucose were measured with an autoanalyzer (Technician RA 2000 Autoanalyzer, Bayer Diagnostic, Mishawaka, IN). Serum insulin levels were measured with the commercial kit IMMULITE 2000 (Siemens Healthcare Diagnostics, Tarrytown, NY). Serum high

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