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Association between perfluoroalkyl substances and reproductive hormones in adolescents and young adults

Meng-Shan Tsai[a], Chien-Yu Lin[b,c], Ching-Chun Lin[a], Mei-Huei Chen[d], Sandy H.J. Hsu[e], Kuo-Liong Chien[f,g], Fung-Chang Sung[h], Pau-Chung Chen[a,i,j,**], Ta-Chen Su[g,j,*]

[a] Institute of Occupational Medicine and Industrial Hygiene, College of Public Health, National Taiwan University, Taipei 100, Taiwan
[b] Department of Internal Medicine, En Chu Kong Hospital, New Taipei City 237, Taiwan
[c] School of Medicine, Fu Jen Catholic University, Taipei County 242, Taiwan
[d] Department of Pediatrics, National Taiwan University Hospital Yun-Lin Branch, Yunlin County 640, Taiwan
[e] Department of Laboratory Medicine, National Taiwan University Hospital, Taipei, Taiwan
[f] Institute of Epidemiology and Preventive Medicine, College of Public Health, National Taiwan University, Taipei 100, Taiwan
[g] Department of Internal Medicine, National Taiwan University Hospital, Taipei 100, Taiwan
[h] Department of Public Health, College of Public Health, China Medical University, Taichung 404, Taiwan
[i] Department of Public Health, National Taiwan University College of Public Health, Taipei 100, Taiwan
[j] Department of Environmental and Occupational Medicine, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei 100, Taiwan

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ABSTRACT

Background: Few studies have explored the association between perfluoroalkyl substances (PFAS) and reproductive hormones in adolescents and young adults.
Objectives: This study aimed to investigate the association of PFAS with reproductive hormones in adolescents and young adults.
Methods: We recruited 540 subjects aged 12–30 years from a 1992 to 2000 mass urine screening population and established a cohort from 2006 to 2008 via invitations by mail or/and telephone. Serum PFAS levels were analyzed with a Waters ACQUITY UPLC system coupled with a Waters Quattro Premier XE triple quadrupole mass spectrometer. Serum reproductive hormone levels were measured by immunoluminometric assay with an Architect random access assay system. PFAS levels were divided into different percentiles according to their detection limits in the multiple regression models to analyze associations between reproductive hormone levels and exposure with PFAS.
Results: The adjusted mean serum level of sex hormone-binding globulin (SHBG) decreased significantly in association with the <50th, 50–75, 75–90 and >90th percentile categories of perfluorooctanoic acid (PFOA) compared with a reference category for the females in the 12–17-year-old group. The follicle-stimulating hormone (FSH) levels were significantly decreased in association with the different percentile categories of perfluorooctane sulfonate (PFOS) in the male 12–17-year-old group and the different percentile categories of perfluoroundecanoic acid (PFUA) in the female 12–17-year-old group. The serum FSH levels in the females aged 12–17 were also decreased in association with the different percentile categories of PFUA. On the other hand, there was a significantly negative association between the different percentile categories of PFOS and the serum testosterone level among the female 12–17-year-old group.
Conclusions: We found that the serum concentrations of PFOA, PFOS, and PFUA were negatively associated with the serum levels of SHBG, FSH, and testosterone in the young Taiwanese population and that these effects were the strongest in the females aged 12–17. Further studies are needed to determine whether these associations are causal.

* Corresponding author at: Department of Internal Medicine, National Taiwan University Hospital, 7 Chung-Shan South Road, Taipei 10055, Taiwan. Tel.: +886 2 23123456x66719; fax: +886 2 23712361.
** Corresponding author at: Institute of Occupational Medicine and Industrial Hygiene, National Taiwan University College of Public Health, #17 Syujhou Road, Taipei 10055, Taiwan. Tel.: +886 2 3366 8088; fax: +886 2 3366 8734.
E-mail addresses: pchen@ntu.edu.tw (P.-C. Chen), tachensu@ntu.edu.tw (T.-C. Su).

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Introduction

Perfluoroalkyl substances (PFAS), such as perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS), are highly bioaccumulative environmental pollutants (Austin et al., 2003) that, which are widely used for both industrial and everyday purposes (Lau et al., 2004). Although food (including migration from packaging and cookware) and drinking water are the primary sources of PFAS exposure in humans, additional exposure routes include air and dust (Haug et al., 2011). Therefore, these substances are widespread in the environment, affecting wildlife and humans (Kannan et al., 2004). In addition, they have been associated with adverse health effects. Until now, the majority of animal studies have associated exposure to PFAS with developmental deficits (Lau et al., 2004), neurotoxicity (Johansson et al., 2008), and immunotoxicity (Keil et al., 2008). Epidemiological research has shown an association among PFAS exposure, child development (Chen et al., 2013), higher thyroid levels (Lin et al., 2013b), and immune system function (Dong et al., 2013).

PFOS and PFOA are well-recognized endocrine disruptors that have antagonistic effects on the synthesis of steroid hormone (Zhao et al., 2010). Reproductive hormones are important for the reproductive system because they play pivotal roles in both male and female puberty development and are crucial to growth and the functioning of a broad range of tissues (Kjeldsen and Bonefeld-Jorgensen, 2013). In general, the average age of the onset of puberty is ten years for girls and twelve years for boys, suggesting that the female onset of puberty occurs earlier than that of males (Sorensen et al., 2012). Few prior epidemiological studies have investigated the impact of PFAS on the human reproductive system, and results have been inconsistent. J. Joensen et al. selected 247 healthy young Danish men with a median age of 19 years to examine the association between reproductive hormones, semen quality and PFAS in the general population (Joensen et al., 2013). They found that the serum PFOS concentration was negatively associated with testosterone levels. Additionally, Lopez-Espinosa et al. have demonstrated that the delay of puberty in children is correlated with PFOS and PFOA levels based on the level of testosterone or oestradiol and the self-reported status (Lopez-Espinosa et al., 2011). A nested case–control study reported that PFAS exposure during pregnancy was not associated with age at menarche in a British cohort (Christensen et al., 2011). Furthermore, a recent study of a pregnant Danish cohort has found that higher levels of PFOA exposure *in utero* may be associated with a later age of menarche compared with lower levels of exposure (Kristensen et al., 2013). In animals, PFOA has been associated with decreased serum testosterone levels in Leydig cell adenomas (Cook et al., 1992) and increased oestradiol levels in rodents (Biegel et al., 1995). The mechanism of the endocrine-disrupting activities of PFAS has been discussed by Lau et al., who have reported that this estrogenic effect is mediated via the oestrogen receptor pathway (Lau et al., 2007).

Studies investigating the impact of PFAS on human reproductive health are limited and controversial and have mainly focused on PFOA and PFOS. Furthermore, there are few studies investigating the health effects of PFAS in adolescents. Therefore, the aim of this study was to assess the association between PFAS and reproductive hormones in young adolescents and young adults.

Materials and methods

Subjects and data collection

The study groups were established from a 1992–2000 mass urine screening population of individuals attending grades 1–12 in Taiwan (Wei et al., 2003). From 2006 to 2008, we invited students in the Taipei area to participate in the study and a follow-up health examination at the National Taiwan University Hospital. Trained assistants and nurses invited these subjects by mail or/and telephone to undergo the health examination and complete a questionnaire. The information has been detailed in previous studies (Lin et al., 2013a,b; Su et al., 2014). Out of 7097 subjects living in Taipei, 790 students completed the follow-up health examination, including the collection of a blood sample and the completion of a questionnaire, but we did not measure the serum PFAS or reproductive hormone levels of all of the subjects due to the collection of limited serum samples. Among the 790 students, 145 had an insufficient serum sample volume for PFAS measurement, and an additional 105 had an insufficient reproductive hormone measurement. Thus, 540 subjects with both PFAS and reproductive hormone measurements were included in the final analysis. This study was approved by the Ethics Committee of the National Taiwan University Hospital (Research Ethics Committee, NTUH). All of the participants and their parents (for the child and adolescent participants) signed informed consent documents upon enrolment in the study.

A questionnaire, including patient age, gender, BMI, lifestyle (drinking, eating, and exercise), household income, and dietary intake (high fat and high sugar), were recorded during the follow-up examinations performed from 2006 to 2008. The subjects were separated by gender and were subdivided by age into 12–17-year-old and 18–30-year-old groups according to the clinical (Moore et al., 2013) definition of adolescence as the period from 12 to 17 years of age. Moreover, the general population has been reported to experience puberty between the ages of 10 and 17 years (Parent et al., 2003). Smoking status (active smoker, passive smoker or has never smoked) and alcohol intake (current alcohol consumption or no alcohol consumption) were determined via the questionnaire and categorized. Household income groups were categorized as above 50,000 New Taiwan dollars (NTD) (equivalent to $1600 USD) per month or below. Weight and height were measured during the follow-up health examination. Body mass index (BMI) was determined as the weight (in kilograms) divided by the square of the height (in metres). Exercise was assessed based on the presence or absence of current exercise habits. A high-sugar diet was defined as one in which subjects consumed sweet foods and soft drinks at a frequency of four times a week or more. Subjects that consumed ham, fatty foods, and fast foods at a frequency of four times a week or more were categorized as having a high-fat diet.

Exposure assessment

All of the plasma samples were stored at −80 °C prior to PFAS analysis. A previous study has reported a fast and sensitive ultra-high performance liquid chromatography/tandem mass spectrometry method to determine PFAS levels (Lien et al., 2011). We first analyzed the levels of 12 PFAS, including potassium perfluorohexanesulfonate (PFHxS), perfluoroheptanoic acid (PFHpA), perfluorononanoic acid (PFNA), perfluorooctanoic acid (PFOA), perfluorooctyl sulfonate (PFOS), perfluorodecanoic acid (PFDeA), perfluoroundecanoic acid (PFUA), perfluorododecanoic acid (PFDoA), 2-(N-methyl-perfluorooctane sulfonamido) acetic acid (Me–PFOSA–AcOH), 2-(N-ethylperfluorooctane sulfonamido) acetic acid (Et–PFOSA–AcOH), perfluorohexanoic acid (PFHxA), and perfluorooctane sulfonamide (PFOSA). However, the levels of eight of these PFAS were more than 70% below the limit of quantitation (LOQ). Therefore, only PFOA, PFOS, PFNA, and PFUA were used for the final analysis. The details of the analytical methods have been previously described (Lien et al., 2011; Lin et al., 2013b). The samples were first vortexed for homogeneity for 30 s. An additional 30-s vortex was performed following the addition of 100 μl of 1% formic