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Quantitative bias analysis for epidemiological associations of perfluoroalkyl substance serum concentrations and early onset of menopause

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ABSTRACT

An association between increased serum concentrations of perfluoroalkyl substances (PFAS) such as perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA) and early menopause has been reported (Knox et al., 2011; Taylor et al., 2014). This association may be explained by the fact that women who underwent menopause no longer excrete PFAS through menstruation. Our objective was to assess how much of the epidemiologic association between PFAS and altered timing of menopause might be explained by reverse causality. We extended a published population life-stage physiologically-based pharmacokinetic (PBPK) model of PFOS and PFOA characterized by realistic distributions of physiological parameters including age at menopause. We then conducted Monte Carlo simulations to replicate the Taylor population (Taylor et al., 2014) and the Knox population (Knox et al., 2011). The analysis of the simulated data overall showed a pattern of results that was comparable to those reported in epidemiological studies. For example, in the simulated Knox population (ages 42–51) the odds ratio (OR) for menopause in the fifth quintile of PFOA compared to those in the first quintile was 1.33 (95% CI 1.26–1.40), whereas the reported OR was 1.4 (95% CI 1.1–1.8). Using our model structure, a substantial portion of the associations reported can be explained by pharmacokinetics.

1. Introduction

Perfluoroalkyl substances (PFAS) are synthetic fluorinated chemicals that have many consumer and industrial uses. They have been used as surfactants in the manufacture of fluoropolymers such as polytetrafluoroethylene (Teflon) and as water and oil repellents in fabrics, leather, floor waxes and wax papers. PFAS are stable, resistant to degradation, and found throughout the environment and in tested humans (Lau et al., 2007; CDC, 2016). Exposure to PFAS has been associated with thyroid disease (Melzer et al., 2010), delayed onset of puberty in girls (Lopez-Espinosa et al., 2011), earlier menopause (Knox et al., 2011; Taylor et al., 2014) and other conditions (Steenland et al., 2010). Most epidemiological studies reporting such associations have measured serum concentrations that are considerably lower than those associated with toxicological effects in test animals (Seacat et al., 2002; Jiang et al., 2012; Tucker et al., 2015).

The association between PFAS and natural menopause may be explained on the basis of reverse causation. Reverse causation refers to the direction of cause-and-effect contrary to common presumption. As PFAS are mainly distributed in blood, menses serve as a route of excretion (Wong et al., 2014). Due to the long half-lives of PFAS (Zhang et al., 2013) and their high binding to plasma proteins (Beesoon and Martin, 2015), menopause may have a considerable impact on their blood concentrations. Females who enter menopause earlier (i.e., end of PFAS excretion through menses) would have PFAS blood concentrations greater than those women who enter menopause later. Thus, the association between PFAS concentrations and early menopause reported by Knox et al. (2011) and Taylor et al. (2014) are possibly related to the timing of menopause on PFAS levels rather than PFAS concentrations on the timing of menopause.

We evaluated the association between PFAS and menopause reported in two epidemiological reports (Knox et al., 2011; Taylor et al., 2014)

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with a quantitative bias analysis using a life-stage physiologically-based pharmacokinetic (PBPK) model (Wu et al., 2015) that we extended to include ages around and beyond menopause. Knox et al. evaluated women 18–65 years of age in the C8 Health Study while Taylor et al. evaluated a National Health and Nutrition Examination Survey (NHANES) study population of women 20–65 years of age. PFOS exposures between the two populations were similar; however, PFOA exposures were substantially higher in the Knox study due to contamination of drinking water in six water districts near the DuPont Washington Works facility in Parkersburg, West Virginia.

Previously, a 3 compartment physiological renal resorption pharmacokinetic model was developed for PFOS and PFOA (Andersen et al., 2006; Tan et al., 2008). This model was extended to a complete PBPK model for simulation of rat, monkey and human pharmacokinetics (Loccisano et al., 2011; Loccisano et al., 2012a). Placental and lactational pharmacokinetics of PFOA and PFOS have also been described using PBPK models in the pregnant, lactating, fetal and neonatal rat and human (Loccisano et al., 2012b; Loccisano et al., 2013). These PBPK models have been used to evaluate PFAS epidemiological associations with lower birth weight (Verner et al., 2015) and extended to a life-stage PBPK model to evaluate the epidemiological association between PFAS and delayed menarche (Wu et al., 2015).

The objective of this study was to assess how much of the epidemiologic association between PFAS and altered timing of menopause might be explained by reverse causality. We evaluated the association between PFAS and age at menopause in simulated populations and compared these simulated outcomes with the epidemiological results (Knox et al., 2011; Taylor et al., 2014).

2. Methods

2.1. PFAS PBPK model

We adapted a PFAS life-stage PBPK model (Wu et al., 2015) to describe the physiological changes during menopause (Fig. 1). This model described PFAS pharmacokinetics in females aged 0–85 years.

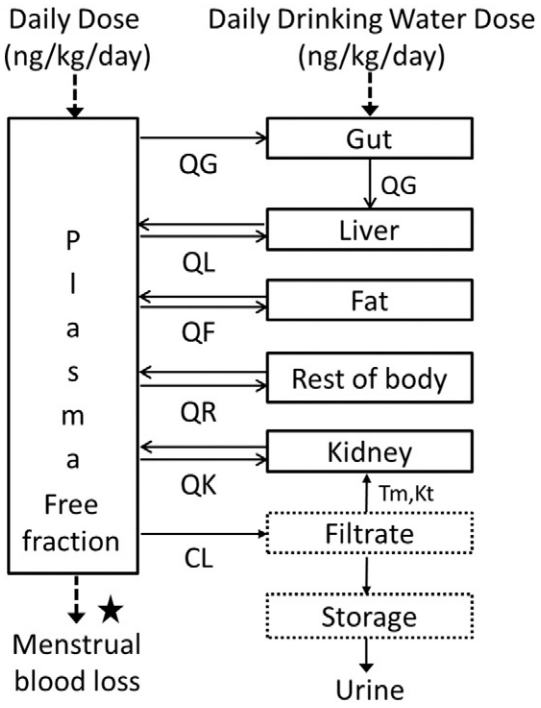

Fig. 1. PFAS PBPK model adapted from Wu et al., 2015 to account for the cessation of menstrual blood loss in menopause. The star indicates the incorporation of equations describing perimenopausal transition and onset of menopause.

The model includes compartments for plasma, gut, liver, fat, rest of body, kidney, filtrate and storage. As the majority of PFAS are bound to albumin in plasma, the concentration of PFAS in plasma and serum is equivalent (Ehresman et al., 2007). Tissue volumes and blood flows were calculated based upon body weight (BW), body height (BH), body surface area (BSA) and body mass index (BMI) as described by Wu et al. An average daily dose was added to the plasma compartment to describe PFOS and PFOA exposure in the Taylor population to account for aggregated daily exposure from multiple sources whereas an average daily drinking water dose was added to the gut compartment to describe PFOA exposure in the Knox population through drinking water, which was by far the dominant exposure in that population. A complete list of chemical- and physiology-specific parameters used for the human female PFAS model can be found in Supplemental materials Appendix A–C. Elimination of total PFAS from the plasma via menstruation began at menarche and ended at menopause, assuming equal PFAS concentration in plasma and menstrual plasma fluid.

2.1.1. Menopausal transition

This transition is generally considered to consist of two stages, early menopausal transition and late menopausal transition, with the main difference being increased irregularity in the late menopausal transition. Early menopausal transition occurs a median of 5.6 years prior to final menstrual period while late menopausal transition occurs a median of 2.6 years prior to final menstrual period (Soules et al., 2001; Paramsothy et al., 2014; Harlow et al., 2006). Final menstrual period is defined as the last menstrual cycle and menopause is defined as 1 year after the final menstrual cycle. Therefore, the age at which early menopausal transition starts (AEMTS) and the age at which late menopausal transition starts (ALMTS) can be defined by the following equations:

$$\text{AEMTS} = \text{age at menopause} - 5.6 \quad (1)$$

$$\text{ALMTS} = \text{age at menopause} - 2.6 + e \quad (2)$$

where e is a random normally distributed number with mean 0.0, standard deviation 3.0 (Harlow et al., 2006), upper limit 2.6 and lower limit −2.6. The bounds prevent implausible ALMTS values (i.e. ALMTS being greater than age at menopause). e was also evaluated as a random normally distributed number with mean 0.0, standard deviation 3.0, upper limit 5.88 and lower limit −5.88. In this alternative method of assigning ALMTS, if ALMTS was greater than age at menopause, ALMTS = age at menopause. Error was incorporated into ALMTS because this transition is accompanied by increased menstrual blood loss per cycle.

2.1.2. Menstrual blood loss per cycle

During late menopausal transition, menses tend to be longer and heavier (Paramsothy et al., 2014) and menstrual blood loss per cycle increases (Hallberg et al., 1966). Using the Hallberg data on menstrual blood loss for 50 year old women and converting the value to a plasma equivalent volume (Verner and Longnecker, 2015), and fitting a lognormal distribution to the expressed volumes from Hallberg, the geometric mean plasma volume equivalent lost per cycle at age 50 years is 54.1 ml, with a geometric standard deviation of 2.29 ml. Thus, beginning at ALMTS, the cycle-specific plasma volume equivalent increases linearly from the baseline of geometric mean 49.9 ml, geometric standard deviation 2.27 ml (Verner and Longnecker, 2015), to corresponding values of 54.1 ml and 2.29 ml by age at menopause.

2.1.3. Menstrual cycle length

The mean menstrual cycle length increases with proximity to final menstrual period (Astrup et al., 2004; Ferrell et al., 2006; Huang et al., 2012). An estimate of premenopausal cycle frequency, 12.5 cycles/year, was obtained from the review by Harlow and Ephross (1995). The best available data on the frequency of cycles in the perimenopausal