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Phthalate metabolite levels and menopausal hot flashes in midlife women

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ABSTRACT

During the menopausal transition, a woman's reproductive capacity declines, her hormone milieu changes, and her risk of hot flashes increases. Exposure to phthalates, which can be found in personal care products, can also result in altered reproductive function. Here, we investigated the associations between phthalate metabolite levels and midlife hot flashes. Eligible women (45–54 years of age) provided detailed information on hot flashes history and donated urine samples ($n = 195$). Urinary phthalate metabolite levels were measured by HPLC–MS/MS. A higher total sum of phthalate metabolites commonly found in personal care products was associated with an increased risk of ever experiencing hot flashes (odds ratio (OR) = 1.45; 95% confidence interval (CI) = 1.07–1.96), hot flashes in the past 30 days (OR = 1.43; 95%CI = 1.04–1.96), and more frequent hot flashes (OR = 1.47; 95%CI = 1.06–2.05). These data suggest that some phthalate exposures from personal care products are associated with menopausal hot flashes in women.

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1. Introduction

Phthalates are a large class of ubiquitous synthetic chemicals, which are used as plasticizers and stabilizers in a myriad of consumer products, including shower curtains, children's toys, cosmetics, and personal care products such as perfumes, nail polishes, deodorants, and lotions [1–3]. Phthalates are also used in pesticides, wood finishes, adhesives, solvents, lubricants, and in medical devices including tubing, blood bags, surgical gloves, and dialysis equipment [1]. The wide range of products in which phthalates are incorporated results in a global production and use of phthalates that is greater than 18 billion pounds per year [1].

The chemical structures of phthalates consist of esters of orthophthalic acid and are named based on the alcohol that generates the varying lengths of the alkyl chain in a linear or branched format. Phthalate esters with long alkyl chains (more than 6 carbons) have higher molecular weights and are likely to undergo chemical modifications for renal excretion. At least six different parent phthalates are used in consumer products, including diethyl phthalate (DEP; short alkyl chain), di(2-ethylhexyl)phthalate (DEHP; long alkyl chain), dibutyl phthalate (DBP; short alkyl chain), diisobutyl phthalate (DiBP; short alkyl chain), diisononyl phthalate (DiNP; long alkyl chain), and butyl benzyl phthalate (BBzP; short alkyl chain) [1,3]. The parent compounds can be converted mainly by the gastrointestinal tract or liver to various metabolites that can be more toxic than the parent compound [1,3–5]. The ubiquity of phthalates and phthalate metabolites is further evidenced by their detection in nearly all tested human urine samples [6–10]. Interestingly, the measured levels of urinary phthalate metabolites are higher in women compared to men [1,11]. This finding is possibly due to a greater use of personal care products by women compared to men.

Previous epidemiological studies indicate that phthalate metabolites can reach the reproductive tissues and adversely affect reproductive function [8,12,13]. For example, phthalate metabolites have been associated with an increased risk of endometriosis [10] and earlier age at menopause [14]. Further, animal studies indicate that exposure to phthalates inhibits ovarian synthesis of sex steroid hormones that are required for normal reproductive function [3,4,15–17], and epidemiological studies indicate that phthalate exposure is associated with reduced sex steroid hormone

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levels [8,12,18,19]. It is not clear, however, whether and how phthalates impact reproductive function as women age and enter the menopausal transition.

During the menopausal transition, a woman's reproductive capacity declines, her hormone milieu changes, and her risk of hot flashes increases [20,21]. Hot flashes are transient periods of intense heat in the upper parts of the body and are often followed by flushing of the skin, profuse sweating, chills, palpitations, and anxiety [22]. Despite the high prevalence of hot flashes among women undergoing the menopausal transition, little is known about the etiology or the risk factors for hot flashes. However, the predominant hypothesis is that drastic changes in estrogen levels lead to the onset of menopausal hot flashes [20,22] and that low estradiol levels are associated with an increased risk of any, frequent, and severe hot flashes [20,23–25].

With evidence from animal studies that phthalates reduce estradiol levels [3,4,15,16], evidence from epidemiological studies that low estradiol levels are associated with an increased risk of hot flashes [20,23,25], and information that women commonly use personal care products containing phthalates [1,2], we tested the hypothesis that higher urinary levels of phthalate metabolites, including those combinations of phthalate metabolites present in personal care products, are associated with an increased risk of midlife hot flashes.

2. Materials and methods

2.1. Ethical approval

All participants gave written informed consent according to procedures approved by the University of Illinois and Johns Hopkins University Institutional Review Boards (file number: 06741).

2.2. Parent study design

Women (primarily Caucasian and African American) residing in Baltimore city (Maryland, USA) and its surrounding counties were enrolled in the Midlife Women's Health Study from 2007 to 2015. Specifically, women with and without natural hot flashes between the ages of 45 and 54 years were invited to participate in a study of women's midlife health by mail. To be eligible for the study, women must not have had a hysterectomy or oophorectomy, and must have been late premenopausal, early or late perimenopausal, and not be pregnant. Women were excluded from the study if they were taking hormone therapy, herbal agents, or other natural agents for treatment of menopausal symptoms, taking oral contraceptives, being treated for any cancer, or postmenopausal. Menopausal status was defined as follows: pre-menopausal women were those who experienced their last menstrual period within the past 3 months and reported 11 or more periods within the past year. Perimenopausal women were those women who experienced: (1) their last menstrual period within the past year, but not within the past 3 months or (2) their last menstrual period within the past 3 months and experienced 10 or fewer periods within the past year. Postmenopausal women were those women who had not experienced a menstrual period within the past year.

Eligible women were invited to the clinic site at Johns Hopkins University. At the clinic visit, women had their weights and heights recorded to calculate their body mass index (BMI). Women also donated spot urine samples for measurements of phthalate metabolites and they donated blood samples for measurements of sex steroid hormone levels. Further, women were asked to complete a detailed questionnaire that included questions regarding their hot flashes history along with additional demographic, medical and reproductive history, and lifestyle information. Hot flashes status was determined based on women's answers on the questionnaires (see Section 2.3). Overall, in the current study, a sample of 195 participants (96 with hot flashes and 99 without hot flashes) was evaluated for urinary phthalate metabolite levels. Additional details related to the study design, recruitment of study participants, and hormone measurements are described in Gallicchio et al. [23].

2.3. Assessment of hot flashes

On the study questionnaires, hot flashes were defined for participants as "a sudden feeling of heat in the face, neck, or upper part of the chest. Hot flashes are often accompanied by reddening or flushing of the skin followed by sweating and chills." At baseline, a detailed hot flash history was obtained through a series of questions on the survey that asked for information on the following: whether the woman had ever experienced hot flashes, whether she had a hot flash in the past 30 days, the usual severity of hot flashes, the frequency of hot flashes, and the length of time that the woman experienced hot flashes. Women who responded no to ever experiencing hot flashes were prompted to skip the more detailed hot flash questions and were categorized as "never experiencing hot flashes". The selected hot flashes questions have been used to collect data on hot flashes in the Midlife Health Studies for over 10 years [23–27].

In terms of severity, each woman was asked to describe her hot flashes as: mild (sensation of heat without sweating), moderate (sensation of heat with sweating), or severe (sensation of heat with sweating that disrupts usual activity). In terms of frequency of hot flashes, each woman was asked to describe her hot flashes as occurring: every hour, every 2–5 h, every 6–11 h, every 12–23 h, 1–2 days per week, 5–6 days per week, 2–3 days per month, 1 day per month, less than 1 day per month, or never. For analysis of the data, the following hot flash variables were examined as dependent variables (outcomes): ever experienced hot flashes (yes versus no); experienced any hot flashes in the past 30 days (yes versus no); moderate or severe hot flashes (yes versus no); and daily hot flashes (yes versus no).

2.4. Measurement of phthalate metabolites

Urine samples were analyzed by isotope dilution high-performance liquid chromatography negative-ion electrospray ionization-tandem mass spectrometry (HPLC–MS/MS) at the Environmental Health Laboratory & Trace Organics Analysis Center, School of Public Health at the University of Washington as previously described [10,28]. The following metabolites were measured: mono-(2-ethyl-5-carboxypentyl)phthalate (MECPP), monobutyl phthalate (MBP), monoethyl phthalate (MEP), mono-(2-ethyl-5-oxohexyl)phthalate (MEOHP), mono-benzyl phthalate (MBzP), mono-isobutyl phthalate (MiBP), mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), and mono-2-ethylhexyl phthalate (MEHP). These phthalate metabolites were selected because they are the major urinary metabolites of common phthalate parent compounds DEP, DEHP, DBP, DiBP, and BBzP [6,8,9,29]. Further, the selected metabolites or their parent compounds have been associated with adverse reproductive outcomes in animal models and epidemiological studies [1,3–5,12,16–18,30–32]. All values (ng/mL) were normalized to the specific gravity value of the sample to account for any potential hydration differences between the participants and volume of the donated sample as described in other studies [33–35]. In cases in which values were lower than the limit of quantitation (LOQ) of the assay, a value of LOQ/square root 2 was assigned to the sample [36].

Humans are exposed to mixtures of phthalates that can contain different parent compounds or metabolites. These parent com-

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