ARTICLE

Determinants of urinary dialkyl phosphate metabolites in midlife women: the Study of Women's Health Across the Nation Multi-Pollutant Study (SWAN-MPS)

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BACKGROUND: Biomonitoring data and determinants of urinary dialkylphosphate (DAP) metabolites, markers of organophosphate pesticides, in racially diverse, non-occupationally exposed populations are scarce.
OBJECTIVE: This study evaluated urinary concentrations and potential determinants of DAP metabolites of organophosphate pesticides in a multi-site, multi-racial/ethnic cohort of women aged 45–56 years, the Study of Women's Health Across the Nation Multi-Pollutant Study (SWAN-MPS).
METHODS: We analyzed 963 urine samples collected in 1999–2000, the baseline of SWAN-MPS for longitudinal studies, and quantified DAP metabolites, including dimethyl alkylphosphates (DMAPs): dimethylphosphate (DMP), dimethylthiophosphate (DMTP), dimethyldithiophosphate (DMDTP); and diethyl alkylphosphates (DEAPs): diethylphosphate (DEP), diethylthiophosphate (DETP), diethyldithiophosphate (DEDTP), using gas chromatography and triple quadrupole mass spectroscopy. Adjusted least squared geometric means (LSGMs) and 95% confidence intervals (CIs) were computed to compare DAP concentrations by socio-demographic, behavioral and dietary factors.
RESULTS: The geometric means (geometric standard deviations) of total DAPs, DMAPs, and DEAPs were 141 (2.63) nmol/L, 102 (2.99) nmol/L, and 26.8 (2.46) nmol/L, respectively. Body mass index (BMI) was inversely associated with DMAPs and DEAPs: LSGM (95% CI) = 68.8 (55.7–84.9) and 21.0 (17.7–25.0) nmol/L for women with obesity vs. 102 (84.7–123) and 30.1 (25.7–35.1) nmol/L for women with normal/underweight, respectively. Fruit consumption was positively (74.9 (62.1–90.2) for less than 5–6 servings/week vs. 105 (84.8–130) nmol/L for 1 serving/day and more) whereas meat consumption was inversely associated with DMAPs (110 (95.0–128) for seldom vs. 82.3 (59.5–114) nmol/L for often consumption). Fresh apple consumption appears to be attributed to the DMAP differences. Alcohol consumption was positively associated with DEAPs (27.5 (23.1–32.7) for 2 drinks/week and more vs. 23.0 (20.0–26.6) nmol/L for less than 1 drink/month). Black women had higher concentrations of DEAPs compared with White women (27.3 (21.2–35.2) vs. 23.2 (20.2–26.7) nmol/L).
IMPACT STATEMENT: Organophosphate pesticides (OPs) are synthetic chemicals and currently the most widely used type of insecticides. We examined multi-site, multi-ethnic cohort of midlife women in the U.S. that offers a unique opportunity to evaluate major determinants of OP exposure. We improved OP metabolite detection rates and obtained accurate concentrations using an improved analytical technique. Our findings suggest that consumptions of fruit, meat and alcohol are important determinants of OP exposure for midlife women. Higher concentrations of diethyl OP metabolites in Black women compared to White women, even after accounting for dietary intake, suggests additional, but unknown racial-ethnic differences that affect exposure.

Keywords: Organophosphate pesticide; dialkyl phosphate metabolites; determinants; midlife women

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INTRODUCTION

Organophosphate pesticides (OPs) are synthetic chemicals and currently the most widely used type of insecticides [1]. Based on the agricultural OP usage estimates for 2017, approximately 16–28 million pounds of the OPs are used annually in the United States [2]. OPs are used in countless settings beyond agriculture including gardens, parks, golf courses, and homes, and these chemicals are widely detected in the environment [3, 4]. The World Health Organization estimates that approximately 8 million people are afflicted with OP exposure-related diseases each year [5]. Due to their toxicity, the production and use of several OPs, including chlorpyrifos and parathion, have been banned [6]. Many types of OPs, however, remain in production and use [6]. Other organophosphate compounds

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are used as flame retardants and also are widely spread in the environment [7].

OPs act as neurotoxins by inhibiting acetylcholinesterase (AChE), a key enzyme responsible for the breakdown of neurotransmitter acetylcholine [8]. Animal studies have shown that OP exposure, even at low doses relevant for human exposure, can induce cognitive impairments [9, 10], neurobehavioral changes [11], and psychological disorders [12]. Low-dose OP exposure also can affect the reproductive system and thyroid hormone levels [13–15], induce oxidative stress [16, 17], and alter neuronal development [18]. In addition, early life exposure to OP has been associated with a variety of adverse health effects in childhood, including intellectual development, neurodevelopment, childhood leukemia, respiratory outcomes, and hypospadias [19]. However, the precise mechanisms through which OPs affect human health remain poorly understood.

Exposure to OPs can occur by inhalation, consumption of water and food, and dermal absorption [20]. OPs are rapidly absorbed and distributed via blood throughout the body, and lipophilic OPs can accumulate in fatty tissues [21]. Enzymes in the liver promote OP decomposition and detoxification [22] and facilitate excretion of OP metabolites through urine [23]. In humans, elimination half-lives of most OPs are short, for example, 24–96 h for diazinon [24] and 3 h for malathion [25]; other OPs are lipophilic and may stay in the body for days to weeks [26–28]. Over 70% of OPs are metabolized into six dialkyl phosphate (DAP) metabolites that are excreted through urine [29]. These urinary DAP metabolites are considered biomarkers of OP exposure.

Several determinants of OP exposure in the general population have been reported. In the US, higher urinary DAP concentrations were associated with younger age, but no significant differences were observed by sex or race/ethnicity [30]. Among pregnant women in Canada, fruit and grain intake, time of urine collection (i.e., evening hours), winter season, non-smoking status, being underweight or normal weight, nulliparous women, and higher education were identified as important determinants of urinary DAP concentrations [31]. Several of these factors were reported for pregnant women in the Netherlands, e.g., urinary DAP concentrations were associated with fruit intake, summer season, smoking cessation, high income, high education, being underweight or normal weight, marital status, and older age [32]. Urinary DAP concentrations have been associated with diet (especially vegetable and fruit intake), body mass index (BMI), social-economic status, smoking, and education in other studies [33–35]. Overall, a number of determinants of OP exposure have been identified, but inconsistencies among the studies suggest that determinants vary by population, location and potentially other factors.

The present study investigated urinary DAP concentrations as biomarkers of OP exposure and their determinants in a large multi-site, multi-racial/ethnic cohort of women aged 45–56 years at the time of sample collection. Drawn from the Study of Women's Health Across the Nation Multi-Pollutant Study (SWAN-MPS), the study sample includes four racial/ethnic groups (White, Black, Chinese, Japanese) residing at five US sites (Oakland, California; Los Angeles, California; Southeast Michigan; Pittsburgh, Pennsylvania; and Boston, Massachusetts). Potential determinants, including socioeconomic, lifestyle, dietary, geographical and demographic characteristics, were evaluated in this large cohort, which includes Chinese and Japanese populations in the US, which have not been examined previously.

MATERIALS AND METHODS

Study population

The SWAN is a longitudinal study designed to address the health effects of menopause and risk factors for age-related chronic diseases. Between 1996 and 1997, 3302 women participants were recruited from 7 sites (Oakland, CA; Los Angeles, CA; Southeast Michigan, MI; Pittsburgh, PA; Boston, MA; Newark, NJ; Chicago, IL) in the US. Eligibility criteria for participants at enrollment included: age 42–52 years; at least one menstrual period in the previous 3 months; no use of exogenous hormones affecting ovarian function in the past 3 months; an intact uterus and at least one ovary; and self-identification with the racial/ethnic groups assigned to the site. Urine specimens were collected in a polypropylene sterile cup before 9 am but were not necessarily first voided urine. Samples were stored at −80 °C until analysis. All participants signed a study consent form, and institutional review board approvals were received at each study site. As part of the SWAN-MPS which was initiated in 2016 to investigate the roles of multiple environmental pollutants in reproductive and metabolic health outcomes in midlife women, we utilized urine samples collected during the third follow-up visit (SWAN-MPS baseline 1999–2000). Women from Chicago and Newark were not included because urine samples were not collected at these sites. After excluding women with insufficient urine samples, a total of 1400 women were included in the SWAN-MPS. For the present study, we excluded 327 samples that did not meet our quality assurance/quality control (QA/QC) criteria (see the next section for more details) and 110 samples with missing information in covariates, yielding 963 samples for data analysis.

Urinary dialkyl phosphate (DAP) analysis

Target OP metabolites included six DAPs which are stable and representative OP biomarkers [36]: dimethylphosphate (DMP), dimethylthiophosphate (DMTP), dimethyldithiophosphate (DMDTP), diethylphosphate (DEP), diethylthiophosphate (DETP), and diethyldithiophosphate (DEDTP). Each 1.5 mL urine sample was spiked with 15 µL of the internal standard, lyophilized using a freeze dryer (Labconco Corporation, MO, USA) for 16 h, then 2 mL of acetonitrile (Fisher Scientific, PA, USA) and 2 mL of diethyl ether (Sigma-Aldrich, MO, USA) were added and mixed (10 min, 200 rpm). After separation of layers, the supernatant was transferred to a new tube, 1 mL of acetonitrile added, and the separation repeated. The supernatant was concentrated under nitrogen gas to 1.5 mL, after which 25 mg of potassium carbonate (Fisher Scientific, PA, USA) and 100 mL of 2,3,4,5,6-pentafluorobenzyl bromide (PFBBr; Sigma-Aldrich, MO, USA) were added, and the mixture was heated to 60 °C for 4 h for derivatization. Five mL of bidistilled water (Merck, Darmstadt, Germany) and 5 mL of n-hexane (Fisher Scientific, PA, USA) were added and mixed (10 min, 200 rpm), and the n-hexane layer was separated using a centrifuge and transferred to a new tube. The extraction process was repeated, again using 5 mL of n-hexane. The combined supernatant was evaporated to 100 µL, and toluene (J.T. Baker, NJ, USA) added to the final analytical solution.

Analyses used the isotope dilution technique and gas chromatography and triple quadrupole mass spectroscopy (Agilent 7890B/7010B triple quadrupole GC-MS/MS, Agilent Technologies, CA, USA). 1 µL of the final sample was injected into the GC equipped with a HP-5MS column 30 m length, 0.25 µm film thickness, 0.25-mm i.d. (Agilent Technologies, CA, USA). Helium was used as the carrier gas at 1.5 mL/min. The temperature program started at 80 °C (2 min), ramped to 250 °C (17 °C/min), then to 300 °C (30 °C/min), and held for 6 min. The MS was operated in electron impact (EI) mode for selected ions with a source temperature of 150 °C and ionization energy of 70 eV. The reproducibility and quantification were excellent for five of the six labeled isotopes, but inconsistent for labeled DEP. Thus, the labeled DMP with the same structure was used for quantification of DEP. Labeled DAPs (ES-5547, Cambridge Isotope Labs, MA, USA) were used as internal standards, and native DAPs standard mixture (ES-5548, Cambridge Isotope Labs, MA, USA) was used for the calibration curve.

QA/QC procedures included instrumental and lab blanks, linearity and drift checks, and internal standard recoveries (Table S1). All QA data met US EPA requirements [37]. We followed the modified QA/QC method used in the National Health and Nutrition Examination Survey (NHANES) using blank urine samples (Sigmatrix urine diluent, Sigma-Aldrich, Taufkirchen, Germany) [38]. The limit of detection (LOD), defined as three times the signal to noise ratio using blank urine samples, ranged from 0.007 ng/mL for DMTP to 0.203 ng/mL for DETP (Table S1). For recovery, 10 ng/mL of native standards were spiked in seven QA/QC samples, and recoveries were calculated as relative concentrations to 10 ng/mL after the preparation process. The average background concentration obtained through the blank test was 0.007 ± 0.006 ng/mL. A procedural blank and test sample spiked with 0.75 ng/mL of DAP ($n = 66$) were included in each

sample sequence to confirm contamination, accuracy and precision (Table S2). The blank concentration averaged 0.021 ± 0.024 ng/mL and the spiked test sample recovery averaged 98%. Overall average accuracy and precision were –2.3% and 21%, respectively, within our ± 25% criteria.

As noted above, this method performed well in the method development and in the test, including spiked and other QA/QC checks analyzed over the study. However, subsequent GC/MS runs showed a trend of increasing retention time, peak tailing and occasionally split peaks, effects that appeared to result from the gradual deterioration of the GC column from decomposition products associated with PFBBr derivatizations and halogen acids. Because each GC run included isotope standards for each analyte, peak identification and normalization remained straightforward. However, in the most deteriorated runs, noise increased, peak integration was not necessarily reliable, and sensitivity was lowered, possibly leading to inaccurate quantification. These issues occurred in specific sequences, which typically contained 40–60 samples, along with QA/QC and calibration samples. In consequence, we excluded 327 samples (25% of 1400 total) that were judged to possibly compromise results. The criteria for excluding the samples were as follows; (1) a split or cut sample peak was observed; (2) the area value of the peak of the internal standard was less than 5000 counts; and (3) for each sequence, the concentration of the standard solution analyzed for QC differed by ± 20% or more from the theoretical concentration. To prevent sample bias (batch effects) during the extraction and analysis process, each sample was assigned with a unique barcode number, and prior to extraction, barcode numbers of 40–60 samples were randomly selected. While the sample sequence was randomized, we found that women excluded due to the compromised results were more likely to be White and Japanese women from Boston and Los Angeles who had their urine collected for DAP assessment in spring and summer (Table S3). No differences were found for other covariates, e.g., BMI, education, smoking status, physical activity, alcohol consumption, and dietary intake.

Covariates

Information on site (Southeast Michigan, MI; Boston, MA; Oakland, CA; Los Angeles, CA; Pittsburgh, PA), race/ethnicity (White, Black, Chinese, Japanese), education (≤ high school; > high school; college; post-graduate), difficulty in paying for basics (very or somewhat hard; not hard at all) was collected at the baseline interview. Sampling seasons were classified into winter (December, January, February), spring (March, April, May), summer (June, July, August), and autumn (September, October, November). Smoking status (never, former, current), passive smoking exposure (0 hours/week; 1–4 hours/week; 5+ hours/week), alcohol consumption (<1/month, ≥1/month and <2/week, ≥2/week), and occupation were self-reported. Weight (kg) and height (m) were measured using standard protocols, and BMI was calculated as kg/m^2. BMI groups were classified into normal or underweight (BMI < 25 kg/m^2), overweight (25–29.9 kg/m^2), and obese (≥30 kg/m^2). Menopausal status (postmenopause (natural or surgery), perimenopause, premenopause, unknown due to hormone therapy) was determined using longitudinal questionnaires assessing bleeding patterns. Total physical activity was assessed using a modified Kaiser Physical Activity Survey to determine the physical activity levels in household/caregiving, occupation, active living, and sports/exercise during the past 12 months (score from 3 to 15) and categorized into tertiles: score ≤6.95, 6.95–8.5, >8.5. Total calorie intake and individual food intake were collected at baseline using a modified Block food frequency questionnaire (FFQ) [39]. We examined intake of vegetables, fruit, cereals, and meat as potential sources of OP exposure. Participants were classified into three groups based on the frequency of each intake: total calorie intake (≤1462.3, 1462.3–1951.3, >1951.3 kcal), vegetables (≤5–6 times/week, >5 − 6 times/week and ≤ 2/day, > 2/day), fruit (<5–6/week, ≥5–6/week and <1/day, ≥1/day), cereals (≤5–6/week, >5 − 6/week and ≤ 2/day, >2/day), and meat (seldom, sometimes, often) consumption. Given that insecticides are widely used on fruit [40, 41], we additionally examined individual fruits (apple, apple juice, prune, peach, canned peach, orange, cantaloupe, mango, watermelon, and strawberry), which were categorized into two or three groups based on intake frequencies.

Statistical analysis

DAP concentrations below the LOD were replaced with the LOD/√2 [42]. To account for urine dilution, DAP concentrations were adjusted for specific gravity (SG) [43]: $DAP_{SG} = DAP_{measured} \times [(SG_{Med} - 1) / (SG_{measured} - 1)]$ where SG_{Med} is the median SG (1.017) of the SWAN participants. We also computed creatinine-adjusted DAP concentrations for comparison. Since the methyl- and ethyl-containing metabolites are derived from O,O-dimethyl- and diethyl-substituted OP pesticides, respectively, their concentrations were converted to molar equivalents and summed to produce the composite dimethyl alkylphosphate (DMAP) and diethyl alkylphosphate (DEAP) concentrations for each participant [30]. We also computed total molar sum of DAPs.

Since DAP concentrations were not normally distributed, we log-transformed DAP variables and computed geometric means (GMs), geometric standard deviations (GSDs), and percentiles. Spearman's rank correlation coefficients were computed to evaluate the correlations between the DAP metabolites.

Multiple linear regression analyses were performed on pre-selected potential determinants (BMI, race/ethnicity, site, education, difficulty in paying for basics, occupation, sampling season, alcohol consumption, smoking status, passive smoking exposure, menopausal status, total physical activity, total calorie intake, and frequencies of consumption of vegetables, fruit, cereals, and meat) and log-transformed individual DAP metabolites as the outcomes. The regression parameters (β coefficients) were back transformed (i.e., exponentiated) to calculate adjusted least squared geometric means (LSGMs) and 95% confidence intervals (CIs). Continuous age was adjusted for as a covariate but LSGMs for different age groups were not computed because of the small range of age (45–56 years). Type-3 analysis of variance (ANOVA) were used to determine significant differences in concentrations by each determinant. Multicollinearity was evaluated using the variable inflation factor (VIF). We employed the conventional p value of 0.05 to identify important determinants of urinary concentrations of DAPs. It should be noted that we do not use this threshold as an indicator of 'statistical significance', and we refrain from interpreting the results with p values > 0.05 as null associations (i.e., no difference in urinary DAP concentrations across different categories) [44].

To determine which type of fruit contributed to urinary concentrations of DAPs, we ran multiple regression with individual fruits (apple, apple juice, prune, peach, canned peach, orange, cantaloupe, mango, watermelon, and strawberry) with adjustment for age, BMI, site, race/ethnicity, education, difficulty in paying for basics, sampling season, alcohol consumption, smoking status, passive smoking exposure, menopause status, total physical activity, total calorie intake. Adjusted LSGMs and 95% CIs were computed.

All statistical analyses were performed using SAS version 4.2 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Distributions of DAPs

Urinary DAP concentrations adjusted for specific gravity and creatinine are summarized in Table 1 and Table S4, respectively. DMP, DMTP, DMDTP, and DEP were detected in all samples with GMs (GSDs) of 7.09 (2.81) ng/mL, 4.66 (3.86) ng/mL, 0.67 (3.65) ng/mL, and 2.86 (2.59) ng/mL, respectively. DETP showed lower detection frequencies (89%) and much lower levels (GMs of 0.97 (3.08) ng/mL). DEDTP was rarely detected (3%), therefore, was not included in subsequent analyses. The GMs (GSDs) of DMAP, DEAP, and $\sum_5$ DAPs were 102 (2.99) nmol/L, 26.8 (2.46) nmol/L, and 141 (2.63) nmol/L, respectively. DAP metabolites were positively and significantly correlated, especially among DMAPs (Spearman rho = 0.58–0.80; Fig. 1), whereas DEP and DETP had a relatively moderate positive correlation (Spearman rho = 0.44). There were weak to moderate correlations between DMAP and DEAP metabolites (Spearman rho=0.24–0.48).

Urinary concentrations of DAP metabolites by characteristics

The adjusted LSGMs and 95% CIs of DAP metabolites by characteristics are shown in Table 2. BMI was inversely associated with all DAP metabolites except DMDTP: LSGM (95% CI) of DMAPs and DEAPs were 93.5 (74.0–118) and 28.0 (23.1–33.9) nmol/L for obese, 140 (113–176) and 36.0 (29.9–43.2) nmol/L for overweight, and 140 (113–173) and 40.2 (33.7–47.9) nmol/L for normal/underweight groups, respectively. Race/ethnicity was associated with DEAPs: LSGM (95% CI) of DEAPs was 23.2 (20.2–26.7) nmol/L for White, 29.4 (24.8–34.8) nmol/L for Black, 23.7 (18.1–31.1) nmol/L for Chinese, and 27.3 (21.2–35.2) nmol/L for Japanese, and the

Table 1. Distributions of DAP concentrations adjusted for specific gravity.

Analyte	Detection frequency (%)	LOD	GM	GSD	Percentiles					
					5th	25th	50th	75th	95th	Maximum
DMP (ng/mL)	100	0.010	7.09	2.81	1.33	3.58	7.24	14.1	36.9	162
DMTP (ng/mL)	100	0.014	4.66	3.86	0.60	1.70	4.49	11.6	44.7	245
DMDTP (ng/mL)	100	0.007	0.67	3.65	0.11	0.24	0.48	1.31	7.45	72.3
DEP (ng/mL)	100	0.029	2.86	2.59	0.63	1.51	2.76	5.33	15.6	56.0
DETP (ng/mL)	89	0.203	0.97	3.08	<LOD	0.47	0.93	1.91	6.87	42.7
DEDTP (ng/mL)	3	0.164	–	–	<LOD	<LOD	<LOD	<LOD	<LOD	8.43
DMAP (nmol/L)	–	–	102	2.99	18.2	48.4	97.5	214	626	2528
DEAP (nmol/L)	–	–	26.8	2.46	6.02	14.8	26.1	46.6	132	464
DAP (nmol/L)	–	–	141	2.63	30.2	70.6	133	272	707	2693

LOD limit of detection, *GM* geometric mean, *GSD* geometric standard deviation, *DMP* dimethylphosphate, *DMTP* dimethylthiophosphate, *DMDTP* dimethyldithiophosphate, *DEP* diethylphosphate, *DETP* diethylthiophosphate, *DEDTP* diethyldithiophosphate, *DMAP* dimethyl alkylphosphate, *DEAP* diethyl alkylphosphate, *DAP* dialkylphosphate.

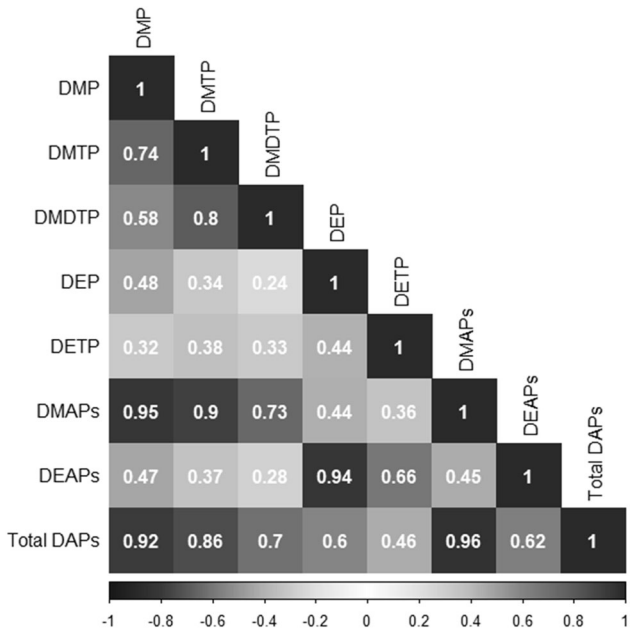

Fig. 1 Spearman correlation coefficients for DAPs displayed using a heat map. DMP dimethylphosphate, DMTP dimethylthiophosphate, DMDTP dimethyldititiophosphate, DEP diethylphosphate, DETP diethylthiophosphate, DMAP dimethyl alkylphosphate, DEAP diethyl alkylphosphate, and DAP dialkylphosphate. DEDTP is excluded due to a low detection rate (3%).

concentrations of DEAPs in Blacks were significantly higher than those in other races. Alcohol consumption was positively associated with DEP and DEAPs: LSGM (95% CI) of DEP and DEAPs were 2.40 (2.06–2.80) ng/mL and 23.0 (20.0–26.6) nmol/L for the low frequency of alcohol consumption (<1/month), 2.88 (2.40–3.45) ng/mL and 27.1 (22.8–32.2) nmol/L for the middle frequency (≥1/month and <2/week), and 2.82 (2.34–3.39) ng/mL and 27.5 (23.1–32.7) nmol/L for the high frequency (≥2/week), respectively. Fruit consumption was positively associated with DMP, DMTP, DETP, DMAPs, and $\sum_5$DAPs: LSGM (95% CI) of DMAPs and $\sum_5$DAPs were 74.9 (62.1–90.2) and 106 (89.9–125) nmol/L for the low frequency of fruit consumption (<5–6/week), 92.7 (76.8–112) and 131 (111–155) nmol/L for the middle frequency (≥5–6/week and <1/day), and 105 (84.8–130) and 146 (121–176) nmol/L for the high frequency (≥1/day), respectively. Meat consumption was inversely associated with DMP, DMTP, DMDTP, DMAPs, and $\sum_5$DAPs: LSGM (95% CI) of DMAPs and $\sum_5$DAPs were 110 (95.0–128) and 150 (132–171) nmol/L for low frequency of meat consumption, 80.3 (65.6–98.3) and 116 (97.1–139) nmol/L for the middle frequency, and 82.3 (59.5–114) and 116 (87.4–155) nmol/L for the high frequency, respectively. However, we found relatively weak associations between DAP exposure markers with site, education, hardship to pay for basics, season, total physical activity, menopause status, smoking status, passive smoking exposure, total calorie intake, vegetable and cereal consumption.

All predictors, with the exception of site and race/ethnicity, exhibited VIF values close to 1, indicating minimal multicollinearity among these covariates (Table S5). It should be noted that the elevated VIF values observed for site and race/ethnicity were anticipated, given the study design that one pre-specified minority racial/ethnic group was recruited at each site.

Since fruit intake was confirmed to be a major determinant of OP exposure, the association between each type of fruit intake frequency and OP exposure was evaluated (Table 3). Fresh apple was positively associated with DMTP, DMDTP, DMAPs, and $\sum_5$ DAPs: LSGM (95% CI) of DMAPs and $\sum_5$DAPs were 77.6 (63.0–95.5) and 115 (95.5–138) nmol/L for the low frequency of fresh apple consumption (<1/week), 81.2 (65.8–100) and 116 (96.5–140) nmol/L for the middle frequency (≥1/week and <3–4/week), and 107 (84.9–134) and 147 (120–180) nmol/L for the high frequency (≥3–4/week), respectively. Mango was associated with DMTP and DETP: LSGM (95% CI) of DMTP and DETP were 3.52 (2.74–4.51) and 0.91 (0.74–1.13) ng/mL for the low frequency of mango consumption (<1/month) and 4.40 (3.39–5.70) and 1.12 (0.90–1.40) ng/mL for the high frequency (≥1/month), respectively. On the other hand, cantaloupe intake showed negative associations with DMP and DMAPs: LSGM (95% CI) of DMP and DMAPs were 6.37 (5.23–7.76) ng/mL and 93.1(75.6, 115) nmol/L for the low frequency of cantaloupe consumption (< 1/week), 6.86(5.62, 8.36) ng/mL and 97.7(79.3, 120) nmol/L for the middle frequency (≥1/week and <3–4/week), and 5.21(4.12, 6.59) ng/mL and 74.0(57.8, 94.7) nmol/L for the high frequency (≥3–4/week), respectively. We found relatively weak associations of DAPs with apple juice, prune, fresh peach, canned peach, orange, watermelon, and strawberry.

To assess the independent roles of geographic location and race/ethnicity, we computed LSGMs of DMAPs and DEAPs by race/ethnicity and site (Fig. 2). Black women had higher concentrations of DMAPs compared with White women in Pittsburgh and had higher concentrations of DEAPs compared with White women in Boston and Pittsburgh. These differences were not observed between Black and White women at the Southeast Michigan site. Further, relatively small differences in DMAPs and DEAPs levels

Table 2. Adjusted least-squared geometric means (95% confidence internals) of DAPs (ng/mL) by characteristics.

	N	DMP	DMTP	DMDTP	DEP	DETP	DMAPs[b]	DEAPs[c]	Σ_5DAPs[a]
BMI									
Normal or underweight	401	7.08 (5.92, 8.47)	4.63 (3.67, 5.83)	0.59 (0.47, 0.74)	3.12 (2.64, 3.68)	1.19 (0.98, 1.45)	102 (84.7, 123)	30.1 (25.7, 35.1)	144 (122, 170)
Overweight	258	7.11 (5.91, 8.55)	4.87 (3.84, 6.18)	0.65 (0.52, 0.82)	2.85 (2.40, 3.38)	0.95 (0.77, 1.16)	104 (85.4, 126)	27.2 (23.2, 31.9)	144 (121, 170)
Obese	304	4.81 (3.94, 5.88)	3.08 (2.38, 3.99)	0.49 (0.38, 0.63)	2.20 (1.82, 2.64)	0.78 (0.63, 0.98)	68.8 (55.7, 84.9)	21.0 (17.7, 25.0)	97.7 (81.2, 118)
p value		**<0.0001**	**0.0002**	**0.05**	**0.0002**	**0.0002**	**<0.0001**	**<0.0001**	**<0.0001**
Race/ethnicity									
White	485	6.08 (5.17, 7.14)	3.79 (3.08, 4.66)	0.56 (0.46, 0.69)	2.48 (2.14, 2.88)	0.87 (0.73, 1.04)	86.1 (72.7, 102)	23.2 (20.2, 26.7)	119 (103, 138)
Black	217	7.47 (6.14, 9.09)	4.02 (3.12, 5.18)	0.51 (0.40, 0.65)	3.17 (2.64, 3.80)	1.01 (0.81, 1.25)	98.0 (79.7, 120)	29.4 (24.8, 34.9)	137 (114, 164)
Chinese	124	5.63 (4.12, 7.68)	4.27 (2.85, 6.38)	0.64 (0.43, 0.95)	2.47 (1.85, 3.30)	0.97 (0.69, 1.37)	86.5 (62.3, 120)	23.7 (18.1, 31.1)	122 (91.6, 163)
Japanese	137	5.91 (4.42, 7.92)	4.39 (3.01, 6.41)	0.59 (0.41, 0.84)	2.71 (2.06, 3.54)	1.01 (0.73, 1.39)	89.8 (66.1, 122)	27.3 (21.2, 35.2)	128 (103, 138)
p value		0.25	0.77	0.78	0.09	0.42	0.71	**0.04**	0.52
Alcohol consumption									
<1/month	504	6.01 (5.10, 7.09)	3.83 (3.09, 4.73)	0.57 (0.46, 0.70)	2.40 (2.06, 2.80)	0.86 (0.72, 1.03)	85.9 (72.2, 102)	23.0 (20.0, 26.6)	119 (102, 139)
≥1/month and < 2/week	228	6.51 (5.34, 7.94)	4.37 (3.38, 5.64)	0.62 (0.48, 0.80)	2.88 (2.40, 3.45)	0.98 (0.79, 1.22)	95.5 (77.5, 118)	27.1 (22.8, 32.2)	134 (112, 161)
≥2/week	231	6.19 (5.06, 7.57)	4.15 (3.20, 5.39)	0.54 (0.42, 0.69)	2.82 (2.34, 3.39)	1.05 (0.84, 1.31)	88.9 (71.9, 110)	27.5 (23.1, 32.7)	126 (105, 152)
p value		0.65	0.47	0.47	**0.04**	0.10	0.50	**0.03**	0.33
Fruit consumption									
<5–6/week	358	5.37 (4.50, 6.41)	3.21 (2.55, 4.04)	0.48 (0.39, 0.60)	2.46 (2.09, 2.90)	0.81 (0.67, 0.98)	74.9 (62.1, 90.2)	23.3 (20.0, 27.2)	106 (89.9,125)
≥5 –6/week and <1/day	352	6.48 (5.42, 7.75)	4.26 (3.38, 5.37)	0.55 (0.44, 0.69)	2.85 (2.42, 3.37)	0.99 (0.81, 1.21)	92.7 (76.8, 112)	27.2 (23.3, 31.7)	131 (111, 155)
≥1/day	253	6.96 (5.68, 8.54)	5.07 (3.90, 6.60)	0.71 (0.55, 0.91)	2.77 (2.30, 3.35)	1.11 (0.89, 1.38)	105 (84.8, 130)	27.1 (22.7, 32.4)	146 (121, 176)
p value		**0.02**	**0.0008**	**0.005**	0.15	**0.009**	**0.003**	0.07	**0.0009**
Meat consumption									
Seldom	752	7.51 (6.52, 8.64)	5.25 (4.38, 6.31)	0.68 (0.57, 0.81)	2.88 (2.52, 3.28)	1.05 (0.90, 1.23)	110 (95.0, 128)	27.4 (24.2, 31.0)	150 (132, 171)
Sometimes	159	5.67 (4.68, 6.88)	3.56 (2.78, 4.57)	0.47 (0.37, 0.62)	2.75 (2.30, 3.28)	0.96 (0.77, 1.18)	80.3 (65.6, 98.3)	26.0 (22.0, 30.8)	116 (97.1, 139)
Often	52	5.69 (4.18, 7.74)	3.71 (2.49, 5.52)	0.59 (0.40, 0.87)	2.47 (1.86, 3.28)	0.88 (0.63, 1.24)	82.3 (59.5, 114)	24.1 (18.4, 31.5)	116 (87.4, 155)
p value		**0.004**	**0.002**	**0.008**	0.52	0.41	**0.002**	0.56	**0.004**
Site									
Southeast Michigan	185	5.61 (4.43, 7.12)	4.04 (2.97, 5.49)	0.56 (0.42, 0.75)	2.46 (1.98, 3.07)	0.92 (0.71, 1.20)	83.5 (65.1, 107)	23.8 (19.3, 29.2)	118 (95.0, 147)
Boston, MA	130	6.43 (5.08, 8.14)	4.47 (3.29, 6.06)	0.61 (0.45, 0.82)	2.89 (2.32, 3.59)	1.08 (0.83, 1.40)	96.1 (75.0, 123)	28.6 (23.3, 35.1)	136 (110, 170)
Oakland, CA	217	6.49 (5.13, 8.20)	3.74 (2.76, 5.07)	0.52 (0.38, 0.69)	2.94 (2.37, 3.66)	0.94 (0.73, 1.21)	88.2 (68.9, 113)	27.6 (22.5, 33.9)	125 (100, 155)
Los Angeles, CA	260	6.01 (4.83, 7.46)	3.91 (2.95, 5.17)	0.58 (0.44, 0.76)	2.55 (2.09, 3.12)	0.87 (0.68, 1.10)	84.6 (67.3, 106)	23.6 (19.6, 28.5)	117 (95.3, 142)
Pittsburgh, PA	170	6.70 (5.35, 8.40)	4.44 (3.32, 5.95)	0.61 (0.46, 0.80)	2.64 (2.14, 3.25)	1.01 (0.79, 1.30)	98.5 (77.6, 125)	25.7 (21.1, 31.3)	138 (112, 170)
p value		0.57	0.82	0.87	0.55	0.60	0.59	0.32	0.43
Education									
≥ High school	172	5.92 (4.83, 7.26)	3.95 (3.04, 5.14)	0.57 (0.44, 0.73)	2.60 (2.15, 3.14)	0.93 (0.74, 1.16)	85.8 (69.3, 106)	24.8 (20.8, 29.7)	122 (101, 148)
< High school	314	6.13 (5.09, 7.39)	3.84 (3.02, 4.88)	0.55 (0.43, 0.69)	2.53 (2.13, 3.01)	0.92 (0.75, 1.13)	87.1 (71.6, 106)	24.6 (20.9, 28.9)	122 (103, 145)
College	236	6.12 (5.02, 7.48)	4.10 (3.17, 5.31)	0.57 (0.45, 0.74)	2.75 (2.28, 3.30)	0.91 (0.73, 1.13)	89.7 (72.7, 111)	25.9 (21.8, 30.8)	126 (105, 152)
Postgraduate	241	6.79 (5.53, 8.34)	4.58 (3.52, 5.98)	0.60 (0.46, 0.78)	2.90, (2.40, 3.51)	1.10 (0.88, 1.38)	97.8 (78.8, 121)	28.0 (23.5, 33.5)	136 (113, 165)
p value		0.59	0.52	0.90	0.45	0.25	0.63	0.42	0.62

Table 2. continued

	N	DMP	DMTP	DMDTP	DEP	DETP	DMAPs[b]	DEAPs[c]	Σ_5DAPs[a]
Hardship to pay for basics									
Very or Somewhat hard	292	6.58 (5.44, 7.96)	4.44 (3.47, 5.67)	0.59 (0.46, 0.75)	2.67 (2.24, 3.19)	0.99 (0.80, 1.22)	95.6 (78.2, 117)	25.7 (21.8, 30.3)	132 (111, 157)
Not hard at all	671	5.90 (5.04, 6.91)	3.81 (3.10, 4.67)	0.56 (0.46, 0.68)	2.71 (2.34, 3.14)	0.93 (0.79, 1.11)	84.7 (71.8, 100)	25.9 (22.6, 29.7)	121 (105, 140)
p value		0.16	0.13	0.56	0.84	0.50	0.14	0.92	0.23
Sampling season									
Winter	195	5.75 (4.68, 7.07)	3.78 (2.89, 4.93)	0.53 (0.41, 0.68)	2.79 (2.31, 3.38)	0.97 (0.77, 1.22)	83.2 (67.0, 103)	26.6 (22.3, 31.9)	120 (99.2, 145)
Spring	272	6.49 (5.39, 7.83)	4.54 (3.57, 5.78)	0.65 (0.51, 0.82)	2.60 (2.19, 3.10)	0.89 (0.72, 1.09)	95.8 (78.7, 117)	24.8 (21.1, 29.2)	130 (110, 155)
Summer	275	6.22 (5.12, 7.54)	3.98 (3.10, 5.11)	0.59 (0.46, 0.75)	2.76 (2.31, 3.30)	1.05 (0.85, 1.29)	88.3 (72.0, 108)	27.0 (22.8, 31.9)	126 (105, 151)
Autumn	221	6.51 (5.35, 7.92)	4.18 (3.25, 5.38)	0.54 (0.42, 0.69)	2.61 (2.18, 3.13)	0.95 (0.76, 1.17)	93.3 (75.9, 115)	24.8 (20.9, 29.4)	130 (108, 155)
p value		0.58	0.49	0.31	0.81	0.43	0.54	0.62	0.81
Total physical activity[a]									
score ≤ 6.95	310	6.19 (5.15, 7.45)	4.12 (3.25, 5.24)	0.56 (0.44, 0.71)	2.57 (2.17, 3.05)	0.96 (0.78, 1.17)	89.6 (73.7, 109)	24.9 (21.2, 29.2)	124 (105, 148)
6.95 < score ≤ 8.5	258	6.06 (5.07, 7.26)	3.85 (3.05, 4.85)	0.52 (0.42, 0.65)	2.91 (2.46, 3.43)	0.97 (0.80, 1.18)	85.5 (70.7, 103)	27.4 (23.5, 32.1)	124 (105, 146)
8.5 < score	304	6.45 (5.33, 7.80)	4.38 (3.42, 5.60)	0.64 (0.51, 0.82)	2.60 (2.18, 3.11)	0.95 (0.77, 1.17)	95.2 (78.0, 116)	25.2 (21.3, 29.7)	131 (110, 157)
p value		0.76	0.48	0.13	0.20	0.97	0.47	0.32	0.70
Menopause status									
Postmenopause (natural or surgery)	132	6.31 (5.03, 7.92)	4.03 (3.01, 5.41)	0.60 (0.45, 0.80)	2.84 (2.30, 3.50)	0.99 (0.77, 1.27)	91.6 (72.2, 116)	26.6 (21.8, 32.4)	130 (105, 160)
Perimenopause	580	6.42 (5.49, 7.52)	4.22 (3.45, 5.16)	0.55 (0.45, 0.66)	2.67 (2.31, 3.08)	0.96 (0.81, 1.14)	92.2 (78.3, 109)	25.6 (22.4, 29.3)	130 (112, 150)
Premenopause	106	5.64 (4.41, 7.20)	3.53 (2.57, 4.85)	0.50 (0.36, 0.67)	2.24 (1.79, 2.82)	0.88 (0.67, 1.16)	78.5 (60.6, 102)	22.3 (18.0, 27.7)	109 (87.1, 137)
Unknown due to hormone therapy	145	6.61 (5.31, 8.23)	4.75 (3.58, 6.31)	0.67 (0.51, 0.88)	3.09 (2.52, 3.78)	1.02 (0.80, 1.30)	98.9 (78.5, 124)	29.1 (24.1, 35.2)	139 (114, 170)
p value		0.65	0.38	0.31	0.09	0.81	0.43	0.17	0.28
Smoking status									
Never	600	6.32 (5.35, 7.48)	4.39 (3.54, 5.46)	0.60 (0.49, 0.75)	2.96 (2.53, 3.45)	1.00 (0.83, 1.20)	94.2 (78.9, 112)	28.3 (24.5, 32.8)	135 (116, 158)
Former	263	6.65 (5.50, 8.03)	4.36 (3.42, 5.57)	0.59 (0.47, 0.75)	2.75 (2.31, 3.28)	0.94 (0.77, 1.16)	95.1 (78.0, 116)	26.1 (22.1, 30.7)	132 (111, 158)
Current	100	5.76 (4.52, 7.35)	3.62 (2.65, 4.97)	0.53 (0.39, 0.72)	2.39 (1.91, 3.00)	0.94 (0.72, 1.23)	81.4 (63.0, 112)	23.2 (18.8, 28.7)	113 (90.3, 142)
p value		0.53	0.47	0.67	0.15	0.77	0.49	0.13	0.29
Passive smoking exposure									
0 hours/week	580	6.07 (5.10, 7.24)	4.18 (3.33, 5.24)	0.60 (0.48, 0.75)	2.63 (2.24, 3.09)	0.94 (0.77, 1.13)	89.4 (74.4, 108)	25.2 (21.6, 29.3)	124 (106, 146)
1–4 hours/week	216	6.16 (5.02, 7.64)	4.04 (3.11, 5.26)	0.55 (0.42, 0.71)	2.62 (2.17, 3.16)	0.97 (0.77, 1.21)	87.8 (70.9, 109)	25.3 (21.2, 30.2)	122 (101, 147)
5+ hours/week	167	6.48 (5.29, 7.95)	4.11 (3.16, 5.35)	0.57 (0.44, 0.74)	2.83 (2.34, 3.42)	0.98 (0.78, 1.23)	92.8 (74.9, 115)	26.9 (22.6, 32.2)	133 (110, 161)
p value		0.82	0.96	0.64	0.72	0.89	0.89	0.74	0.68
Total calorie intake, kcal									
kcal ≤ 1462.3	317	6.22 (5.13, 7.53)	4.12 (3.21, 5.28)	0.56 (0.44, 0.71)	2.57 (2.15, 3.07)	0.95 (0.77, 1.18)	89.7 (73.3, 110)	24.7 (20.9, 29.1)	125 (105, 149)
1462.3 < kcal ≤ 1951.3	309	6.57 (5.46, 7.91)	4.24 (3.33, 5.39)	0.59 (0.47, 0.75)	2.66 (2.24, 3.16)	0.91 (0.74, 1.11)	94.3 (77.6, 115)	25.4 (21.6, 29.9)	130 (109, 154)
kcal > 1951.3	337	5.93 (4.99, 7.06)	3.98 (3.18, 4.98)	0.57 (0.46, 0.71)	2.85 (2.43, 3.35)	1.03 (0.85, 1.25)	86.1 (71.7, 103)	27.3 (23.5, 31.8)	125 (106, 146)
p value		0.47	0.84	0.86	0.39	0.37	0.58	0.35	0.82
Vegetable consumption									
≤5 − 6/week	358	6.32 (5.23, 7.65)	4.27 (3.34, 5.46)	0.60 (0.48, 0.77)	2.80 (2.34, 3.33)	1.04 (0.85, 1.29)	92.3 (75.6, 113)	27.0 (22.9, 31.9)	132 (111, 158)
>5 − 6/week and ≤ 2/day	320	5.84 (4.85, 7.03)	3.84 (3.02, 4.89)	0.53 (0.42, 0.66)	2.56 (2.16, 3.05)	0.95 (0.77, 1.17)	83.6 (68.7, 102)	24.9 (21.2, 29.3)	116 (98.0, 138)
>2/day	285	6.56 (5.47, 7.88)	4.23 (3.34, 5.36)	0.59 (0.47, 0.75)	2.72 (2.30, 3.22)	0.90 (0.73, 1.10)	94.4 (77.9, 114)	25.5 (21.7, 29.8)	131 (111, 155)
p value		0.37	0.55	0.35	0.51	0.30	0.34	0.53	0.17

Table 2. continued

	N	DMP	DMTP	DMDTP	DEP	DETP	DMAPs[b]	DEAPs[c]	Σ_5DAPs[a]
Cereal consumption									
≤5 – 6/week	469	6.54 (5.54, 7.72)	4.05 (3.26, 5.02)	0.55 (0.45, 0.68)	2.73 (2.34, 3.18)	1.03 (0.86, 1.24)	92.5 (77.7, 110)	26.5 (23.0, 30.7)	131 (112, 152)
>5 – 6/week and ≤ 2/day	202	5.95 (4.86, 7.27)	3.71 (2.86, 4.81)	0.55 (0.43, 0.71)	2.59 (2.15, 3.12)	0.93 (0.75, 1.16)	84.1 (68.0, 104)	24.8 (20.9, 29.6)	120 (99.5, 144)
>2/day	292	6.23 (5.15, 7.54)	4.63 (3.61, 5.93)	0.62 (0.49, 0.79)	2.76 (2.31, 3.29)	0.92 (0.75, 1.14)	93.7 (76.6, 115)	26.0 (22.1, 30.8)	129 (108, 154)
p value		0.54	0.19	0.41	0.74	0.34	0.50	0.68	0.55

Concentrations were adjusted for specific gravity (SG).
Adjusted for age, BMI, site, race/ethnicity, education, hardship to pay for basics, sampling season, alcohol consumption, smoking status, passive smoking exposure, menopause status, total physical activity, total calorie intake, and intake frequencies of vegetable, fruit, cereal, and meat. Statistically significant values ($p < 0.05$) were shown in bold.
[a]Σ_5DAPs; Sum of DMP, DMTP, DMDTP, DEP, and DETP.
[b]DMAPs; Sum of DMP, DMTP, and DMDTP.
[c]DEAPs; Sum of DEP and DETP.

were observed between White and Chinese women in Oakland or White and Japanese women in Los Angeles.

DISCUSSION

In this study, we analyzed urinary DAP metabolites, markers of OP exposure, from a multi-site, multi-race/ethnic cohort of women aged 45–56 years of age between 1999 and 2000. We found that BMI, consumptions of fruit, meat, and alcohol, and race/ethnicity are important determinants of OP exposure among midlife women. High consumption of fruit, especially fresh apples, were associated with higher concentrations of dimethyl OPs, whereas high consumption of alcohol was associated with higher concentrations of diethyl OPs. At two of the three sites, Black women had higher urinary concentrations of DEAP compared with White women.

Most OPs are metabolized mainly into DMP, DMTP, and DEP by desulfurization, oxidation and hydrolysis [45]. (EPA-registered OPs and their potential DAP metabolites are shown in Table S6). DMDTP and DEDTP can be further converted into DMP and DEP, respectively [46]. Given the short elimination half-lives (hours to days) of DMAPs and DEAPs [47, 48], the high detection rates suggest continuous exposure to the parent OP compounds. The strong correlations between DAP compounds suggest that these metabolites were derived from the same parent OP compounds (DMP, DMTP, and DMDTP from dimethyl OPs, and DEP and DETP from diethyl OPs) [30]. Generally different types of OPs are used together to increase the efficiency of insect pest control [49].

The median concentrations of DMAP (97.5 nmol/L) and DEAP (26.1 nmol/L) in the present study were much higher than those among adults in the NHANES in 1999–2000 (22.1 and 6.83 nmol/L) [50], however, higher percentile concentrations (e.g., 90th and 95th percentile) were similar. These differences may arise from our enhanced and sensitive analytical technique, which resulted in very high detection rates for most compounds, which could significantly change median levels. The average detection frequency of DAP in NHANES was 58% [30], significantly lower than that in this study (average detection frequency; 98%). This is in part supported by the similarity of the high percentile concentrations, which would be expected to have similar analytical determinations.

Comparing NHANES results in 1999–2000 (medians of DMAP; 22.1 nmol/L, DEAP; 6.83 nmol/L) to those in 2015–2016 (medians of DMAP; 16.1 nmol/L, DEAP; 13.6 nmol/L) [50], DMAP concentrations have decreased, however, DEAP concentrations have increased over time. The average detection rate of NHANES in 2015–2016 was 82% [50], an increase compared to the detection rate in 1999–2000. Due to the lower detection rates of these compounds in NHANES in 1999–2000, the median concentration measurements might be lower than actual concentrations, which would contribute to the apparent increase in the DEAP concentration trend. This is also supported by the decreasing results of both DMAP and DEAP levels suggested by comparing the results of the present study for 1999–2000 with NHANES for 2015–2016.

In 100 pregnant women from the Generation R cohort in the Netherlands during 2004–2006, DAP levels were higher than or comparable to our results, e.g., the median dimethyl alkyl phosphate level was 179 nmol/L, considerably higher than observed in our cohort [51]. This may reflect fruit and vegetable consumption rates [32], which in the Netherlands (296 g/day) considerably exceed US rates (167 g/day) [52, 53], as well as the Netherland's higher intensity of pesticide use (e.g., expressed as kg/km^2 of farmland) than the US and other countries [54] that may lead to the highest concentrations of residual OPs found in foodstuffs in Europe [55]. In addition, 32% of pesticides used in the Netherlands produce dimethyl metabolites, therefore, dimethyl OPs were predominantly detected in foodstuffs [56]. Lower DAP

Table 3. Adjusted least-squared geometric means (95% confidence internals) of DAPs (ng/mL) by individual fruit intake.

	N	DMP (ng/mL)	DMTP (ng/mL)	DMDTP (ng/mL)	DEP (ng/mL)	DETP (ng/mL)	DMAPs[b] (nmol/L)	DEAPs[c] (nmol/L)	Σ_5DAPs[a] (nmol/L)
Fresh apple									
<1/week	425	5.68 (4.66, 6.93)	3.27 (2.53, 4.22)	0.47 (0.37, 0.60)	3.07 (2.56, 3.69)	1.04 (0.83, 1.29)	77.6 (63.0, 95.5)	29.5 (24.8, 35.0)	115 (95.5, 138)
≥1/week and < 3 − 4/week	294	5.76 (4.72, 7.04)	3.65 (2.82, 4.72)	0.50 (0.39, 0.64)	2.59 (2.15, 3.11)	0.92 (0.74, 1.15)	81.2 (65.8, 100)	25.0 (21.0, 29.7)	116 (96.5, 140)
≥3–4/week	244	6.95 (5.59, 8.65)	5.10 (3.85, 6.76)	0.71 (0.54, 0.93)	2.91 (2.38, 3.56)	1.09 (0.86, 1.38)	107 (84.9, 134)	28.2 (23.3, 34.1)	147 (120, 180)
p value		0.06	**0.0007**	**0.0006**	0.08	0.22	**0.002**	0.07	**0.007**
Apple juice									
<1/month	530	6.13 (5.04, 7.46)	3.99 (3.10, 5.13)	0.59 (0.47, 0.76)	2.69 (2.25, 3.23)	1.00 (0.81, 1.24)	88.5 (72.0, 109)	26.5 (22.3, 31.4)	125 (104, 150)
≥1/month and <2 − 3/month	196	5.97 (4.82, 7.41)	3.81 (2.88, 5.03)	0.53 (0.40, 0.69)	2.77 (2.27, 3.38)	0.99 (0.78, 1.25)	86.1 (68.7, 108)	26.8 (22.2, 32.3)	123 (101, 151)
≥2–3/month	237	6.22 (5.03, 7.68)	4.01 (3.05, 5.26)	0.53 (0.41, 0.69)	3.10 (2.55, 3.76)	1.05 (0.83, 1.33)	88.3 (70.7, 110)	29.3 (24.4, 35.2)	127 (105, 155)
p value		0.92	0.91	0.42	0.22	0.82	0.96	0.37	0.95
Prune									
<1/month	831	5.98 (5.02, 7.12)	4.13 (3.29, 5.17)	0.56 (0.45, 0.70)	2.68 (2.28, 3.15)	0.92 (0.76, 1.12)	88.2 (73.4, 106)	25.4 (21.8, 29.5)	124 (105, 146)
≥1/month	132	6.24 (4.96, 7.84)	3.75 (2.79, 5.04)	0.54 (0.40, 0.71)	3.03 (2.45, 3.74)	1.12 (0.87, 1.43)	87.0 (68.4, 111)	29.8 (24.4, 36.3)	127 (102, 157)
p value		0.67	0.46	0.71	0.18	0.08	0.89	0.07	0.80
Fresh peach									
<2–3/month	365	5.58 (4.52, 6.89)	3.71 (2.83, 4.88)	0.52 (0.40, 0.67)	2.83 (2.33, 3.44)	1.13 (0.90, 1.43)	81.4 (65.2, 102)	28.4 (23.7, 34.1)	119 (97.4, 144)
≥2–3/month and <3–4/week	360	6.19 (5.07, 7.56)	4.20 (3.24, 5.44)	0.58 (0.45, 0.74)	2.74 (2.28, 3.30)	1.03 (0.83, 1.29)	89.6 (72.6, 111)	26.7 (22.4, 31.7)	126 (105, 152)
≥3–4/week	238	6.60 (5.33, 8.17)	3.90 (2.96, 5.14)	0.55 (0.42, 0.72)	2.97 (2.44, 3.62)	0.89 (0.70, 1.12)	92.2 (73.6, 115)	27.4 (22.8, 33.0)	131 (107, 159)
p value		0.25	0.51	0.62	0.63	0.10	0.46	0.68	0.57
Canned peach									
<1/month	561	6.37 (5.27, 7.70)	3.93 (3.07, 5.02)	0.54 (0.43, 0.69)	2.84 (2.38, 3.38)	0.97 (0.78, 1.19)	89.1 (73.0, 109)	26.8 (22.7, 31.6)	126 (106, 151)
≥1/month and <2 − 3/month	190	6.08 (4.88, 7.56)	3.83 (2.89, 5.08)	0.56 (0.43, 0.74)	2.88 (2.36, 3.53)	1.01 (0.80, 1.29)	87.5 (69.5, 110)	27.8 (23.0, 33.6)	125 (102, 153)
≥2 − 3/month	212	5.88 (4.74, 7.30)	4.04 (3.06, 5.34)	0.54 (0.42, 0.71)	2.82 (2.38, 3.38)	1.06 (0.84, 1.34)	86.3 (68.8, 108)	27.9 (23.1, 33.6)	124 (101, 151)
p value		0.65	0.92	0.93	0.97	0.61	0.94	0.82	0.97
Orange									
<1/week	369	6.24 (5.04, 7.71)	4.14 (3.14, 5.44)	0.56 (0.43, 0.73)	2.65 (2.18, 3.22)	0.89 (0.71, 1.13)	90.3 (72.2, 113)	25.1 (20.9, 30.2)	124 (102, 151)
≥1/week and <5 − 6/week	420	6.23 (5.15, 7.53)	3.96 (3.10, 5.06)	0.57 (0.45, 0.73)	2.84 (2.38, 3.38)	1.10 (0.89, 1.35)	89.5 (73.2, 109)	28.1 (23.9, 33.2)	129 (108, 154)
≥5 − 6/week	174	5.87 (4.66, 7.38)	3.71 (2.76, 5.00)	0.51 (0.39, 0.68)	3.07 (2.48, 3.79)	1.06 (0.83, 1.37)	83.2 (65.3, 106)	29.4 (24.1, 35.9)	122 (98.8, 151)
p value		0.82	0.76	0.66	0.37	0.09	0.75	0.21	0.81
Cantaloupe									
<1/week	450	6.37 (5.23, 7.76)	4.24 (3.28, 5.47)	0.59 (0.47, 0.76)	2.68 (2.23, 3.21)	0.99 (0.80, 1.23)	93.1 (75.6, 115)	26.3 (22.2, 31.2)	132 (110, 158)
≥1/week and <3 − 4/week	336	6.86 (5.62, 8.36)	4.36 (3.38, 5.63)	0.59 (0.46, 0.76)	3.10 (2.58, 3.72)	1.10 (0.89, 1.37)	97.7 (79.3, 120)	29.6 (25.0, 35.2)	136 (113, 164)
≥3 − 4/week	176	5.21 (4.12, 6.59)	3.29 (2.43, 4.46)	0.47 (0.35, 0.63)	2.78 (2.24, 3.46)	0.95 (0.73, 1.23)	74.0 (57.8, 94.7)	26.6 (21.7, 32.7)	109 (87.9, 136)
p value		**0.03**	0.09	0.16	0.15	0.30	**0.03**	0.22	0.06

Table 3. continued

	N	DMP (ng/mL)	DMTP (ng/mL)	DMDTP (ng/mL)	DEP (ng/mL)	DETP (ng/mL)	DMAPs[b] (nmol/L)	DEAPs[c] (nmol/L)	Σ_5DAPs[a] (nmol/L)
Mango									
<1/month	664	5.94 (4.90, 7.20)	3.52 (2.74, 4.51)	0.52 (0.41, 0.66)	2.78 (2.33, 3.32)	0.91 (0.74, 1.13)	82.4 (67.3, 101)	26.2 (22.2, 31.0)	118 (98.4, 141)
≥1/month	298	6.28 (5.14, 7.68)	4.40 (3.39, 5.70)	0.58 (0.45, 0.75)	2.92 (2.43, 3.51)	1.12 (0.90, 1.40)	93.2 (75.5, 115)	28.9 (24.2, 34.3)	133 (110, 160)
p value		0.51	**0.04**	0.25	0.53	**0.02**	0.16	0.19	0.11
Watermelon									
<2 − 3/month	359	6.18 (5.01, 7.62)	4.34 (3.31, 5.69)	0.63 (0.49, 0.82)	2.82 (2.32, 3.41)	1.09 (0.87, 1.38)	91.7 (73.6, 114)	27.7 (23.1, 33.2)	130 (107, 1580)
≥2 − 3/month and <2/week	310	5.84 (4.77, 7.15)	3.68 (2.84, 4.78)	0.50 (0.39, 0.64)	2.96 (2.45, 3.56)	1.00 (0.80, 1.25)	83.1 (67.2, 103)	28.2 (23.7, 33.6)	121 (101, 146)
≥2/week	292	6.31 (5.01, 7.76)	3.80 (2.91, 4.96)	0.52 (0.40, 0.68)	2.78 (2.30, 3.36)	0.95 (0.76, 1.19)	88.3 (71.1, 110)	26.6 (22.3, 31.8)	124 (103, 151)
p value		0.64	0.30	0.08	0.71	0.39	0.52	0.76	0.69
Strawberry									
<1/week	367	6.04 (4.89, 7.45)	3.78 (2.88, 4.95)	0.56 (0.43, 0.72)	3.02 (2.49, 3.67)	1.03 (0.81, 1.29)	85.8 (68.8, 107)	28.6 (23.9, 34.3)	125 (103, 152)
≥1/week and <3 − 4/week	371	6.08 (4.98, 7.42)	3.92 (3.03, 5.07)	0.51 (0.39, 0.65)	2.81 (2.33, 3.37)	0.96 (0.77, 1.20)	86.8 (70.4, 107)	27.0 (22.7, 32.1)	123 (102, 148)
≥3 − 4/week	221	6.21 (4.99, 7.72)	4.11 (3.11, 5.45)	0.59 (0.45, 0.77)	2.73 (2.23, 3.33)	1.06 (0.83, 1.34)	90.3 (71.9, 114)	26.9 (22.3, 32.5)	127 (104, 156)
p value		0.96	0.82	0.38	0.53	0.60	0.89	0.71	0.97

Concentrations were adjusted for specific gravity (SG).
Adjusted for age, BMI, site, race/ethnicity, education, hardship to pay for basics, sampling season, alcohol consumption, smoking status, passive smoking exposure, menopause status, total physical activity, and total calorie intake.
Statistically significant values ($p < 0.05$) were shown in bold.
[a]Σ_5DAPs; Sum of DMP, DMTP, DMDTP, DEP, and DETP.
[b]DMAPs; Sum of DMP, DMTP, and DMDTP.
[c]DEAPs; Sum of DEP and DETP.

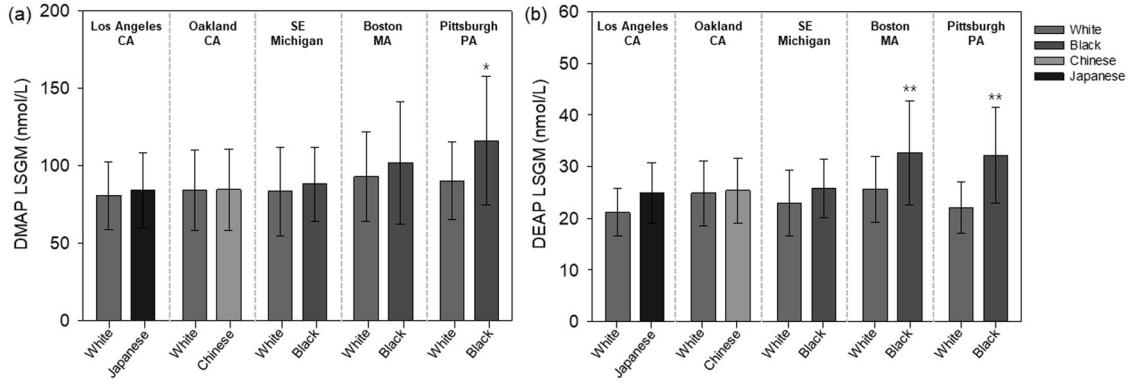

Fig. 2 Least squared geometric means of urinary DAP concentrations by site and race/ethnicity. a, **b** represent DMAPs and DEAPs, respectively.

concentrations were found in other European countries, possibly since the use of certain OPs (e.g., parathion, methyl parathion, sulfotep) has been banned since 2001 [57, 58], while US use continued until 2002 – 2004 [6]. In 573 pregnant women in Spain sampled from 2003 to 2005 [34], DAP levels were lower than US levels, possibly reflecting these use patterns and the impacts of use restrictions. The decrease in DAP concentrations over time and the relatively high OP exposure compared to those in other countries demonstrated the effectiveness and necessity of national regulations for pesticide use and production.

For dietary habits, fruit, meat and alcohol consumption was associated with DAP concentrations, whereas relatively small differences in DAP concentrations were found with vegetable and cereal consumption. In particular, fruit consumption showed a strong positive trend with the concentrations of DAPs, indicating that fruit consumption was a major route of OP exposure. High concentrations of residual OPs in fruits have been reported in previous studies [40, 59]. In addition, alcohol consumption showed a positive trend with DEP and DEAP concentrations. OPs have been detected in wine and beer made from fruits or grains, in particular, diethyl OPs were detected at high concentrations in grape skins and wine [60]. DAP patterns associated with fruit and alcohol consumption reflected the different types of pesticides used in fruit and grains, i.e., fruit consumption strongly related to DMAP while alcohol consumption related to DEAP.

Positive associations between DAP concentrations and fresh apple or mango consumption, and the negative association with cantaloupe consumption, suggest that OP exposure may be affected by the type of fruit, frequency of consumption, method of fruit intake, and consumption of imported fruit. Dimethyl OPs such as azinphos-methyl, dimethoate, fenitrothion, and methidathion mainly used on various fruits [40]. The intake frequency of fresh apple was relatively high compared to other fruits. Apples consumed sometimes or mainly with the peel (fruit skin) had positive associations with exposure to dimethyl OPs. The negative association with dimethyl OP exposure and cantaloupe consumption, for which the rind (skin) is not eaten, suggests that the skin of the fruit can have an important effect on the pesticide exposure. This may be because fruits with thick skins, such as melons and watermelons, are prone to pesticide penetration into their flesh compared to those with thinner skins [61]. In addition, mango is mainly imported from Mexico and India, and OPs are widely used in these countries [62]. In particular, various OPs might be used to increase the persistence of the applied insecticides for long-distance shipment [63].

OP exposure was associated with fresh apple intake, but not with fruits processed into juice or canned products. This may be because much of the residual pesticide remains mainly on the peel of the fruit [40, 59], which was by washing and peeling during processing Therefore, to prevent exposure to pesticides, it is suggested that fruits should be consumed after washing or removing the peel.

BMI and meat consumption consistently showed inverse associations with DAPs. In the present study, high intake of vegetables and fruits was associated with low meat intake (data not shown). Further, higher intake of meat and lower intake of vegetables and fruit have been associated with obesity [64]. In addition, there may be a difference in the metabolism and excretion of chemicals depending on BMI [65]. This inverse association of BMI with OP exposure has been shown in several studies [31, 32]. Therefore, the inverse associations between BMI or meat consumption and OP exposure further support the role of dietary intake as a major route of OP exposure.

This study allowed the evaluations of differential exposure to OPs between White and Black women within the same geographic location (Fig. 2). Concentrations of DAPs in Black women were high relative to the other race/ethnicities. In particular, concentrations of DMAPs and DEAPs in Black women in Pittsburgh and DEAP concentrations in Black women in Boston were higher than those for White women at the same sites. There were no differences between White and Chinese women in Oakland and White and Japanese women in Los Angeles. These patterns were independent of geographic locations. Higher concentrations of DAP metabolites in non-Hispanic Black compared to non-Hispanic White participants were also observed in the NHANES 1999–2000, but differences were not statistically significant [30]. The White/Black differences may indicate differences in exposure sources, particularly since Black women in this study had the lower fruit and alcohol consumption compared to White women (data not shown). The racial differences might be explained by the quality of food (e.g., organic vs. conventional), cultural differences, pesticide use at home, or occupational pesticide exposure. Information regarding these factors was not available in the present study. Additional research is required to identify specific exposure pathways by race.

The present study has several strengths, including its multi-ethnic, community-based cohort and the rich data on potential determinants. We improved DAP detection rates and obtained accurate concentration measurements using an improved analytical technique, and we show that OP exposure may not differ by geographic location. We also recognize several limitations in this study. First, as part of an epidemiological study of the health impacts of OPs, human exposure to OPs was assessed using urine samples collected at baseline, 1999–2000. As confirmed in this study, dimethyl OP exposure has decreased whereas diethyl OP exposure has increased over time in the U.S., and thus the exposure determinants identified may not fully reflect what might be observed using more recent urine samples. Second, information on the use of pesticides at home and in the workplace was not available as the present study utilized an ongoing cohort

study that was not designed to evaluate pesticide use or exposure. Nonetheless, we were able to evaluate a wide range of physiological, socioeconomic, behavioral, environmental, and dietary factors applicable to White, Black, Chinese and Japanese women. We could not evaluate OP exposure in Hispanic women since SWAN-MPS did not include Hispanic women. Third, our findings may not be generalizable to males and age groups other than midlife.

In conclusion, dietary intake of especially fruit, meat and alcohol is an important determinant of OP exposure for midlife women. Higher concentrations of diethyl OP metabolites in Black women compared to White women, even after accounting for dietary intake, suggests additional, but unknown racial-ethnic differences that affect exposure. Further studies are needed to identify racial/ethnic differences in exposure sources of OP and whether the racial/ethnic difference in exposure may contribute to health disparities.

DATA AVAILABILITY

SWAN provides access to public use datasets that include data from SWAN screening, the baseline visit and follow-up visits (https://agingresearchbiobank.nia.nih.gov/). To preserve participant confidentiality, some, but not all, of the data used for this manuscript are contained in the public use datasets. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided. A link to the public use datasets is also located on the SWAN web site: http://www.swanstudy.org/swan-research/data-access/. Investigators who require assistance accessing the public use dataset may contact the SWAN Coordinating Center at the following email address: swanaccess@edc.pitt.edu.

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AUTHOR CONTRIBUTIONS

Sung-Hee Seo was responsible for the measurement of urinary DAPs, data analysis, interpretation of results, and writing—original draft, and revisions. Stuart Batterman oversaw DAPs method development and measurement analysis, laboratory administration, and contributed to results interpretation and manuscript revisions. Carrie Karvonen-Gutierrez contributed to funding acquisition, project administration, and manuscript revisions. Sung Kyun Park is the guarantor of this work and had full access to all the data in the study and takes responsibility for the contents of the manuscript. Sung Kyun Park was responsible for funding acquisition, study design protocols, oversight of statistical analysis, interpretation of results, project administration, and writing.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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