


# BMJ Open Polycyclic aromatic hydrocarbons and risk of rheumatoid arthritis: a cross-sectional analysis of the National Health and Nutrition Examination Survey, 2007–2016

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## ABSTRACT

**Objective** While there are several well-established environmental risk factors for rheumatoid arthritis (RA), a paucity of evidence exists linking environmental toxicants with RA prevalence. We aimed to examine the associations between various environmental toxicants and RA among adults in the U.S. general population while adjusting for non-heritable risk factors.

**Design** Cross-sectional study.

**Setting** National Health and Nutrition Examination Survey conducted from 2007 to 2016.

**Participants** The study included 21 987 adult participants (no RA: 20 569; RA: 1418). Participants were excluded (n=7214) if they did not answer questions related to self-reporting of RA, had another or unknown type of arthritis, or did not have interview or biospecimen data.

**Primary and secondary outcome measures** Association between individual toxicants and body burden scores for polycyclic aromatic hydrocarbons (PAH), phthalates and plasticisers (PHTHTEs) metabolites or volatile organic compounds (VOCs) and participant self-reported RA based on multivariable logistic regression models while adjusting for age, sex, urine creatinine, body mass index, smoking, race, education, family poverty income ratio, any vigorous or moderate activity and dietary fibre.

**Results** While increased prevalence of RA was observed in participants with the highest quartile of various individual PAHs, only 1-hydroxynaphthalene (OR: 1.8 (1.1 to 3.1); p=0.020) remained associated in a fully adjusted model. PAH body burden was found to be associated with RA (Q4 vs Q1, OR: 2.2 (1.09 to 4.2); p=0.028) in a fully adjusted model. Interestingly, after accounting for PAH body burden, smoking was not associated with RA (OR: 1.4 (0.89 to 2.3); p=0.13). A mediation analysis demonstrated that PAH body burden accounted for 90% of the total effect of smoking on RA. PHTHTE and VOC metabolites were not associated with RA in fully adjusted models.

**Conclusions and relevance** PAHs are associated with RA prevalence, mediate the majority of the effects of smoking on RA, and are associated with RA independent of smoking status.

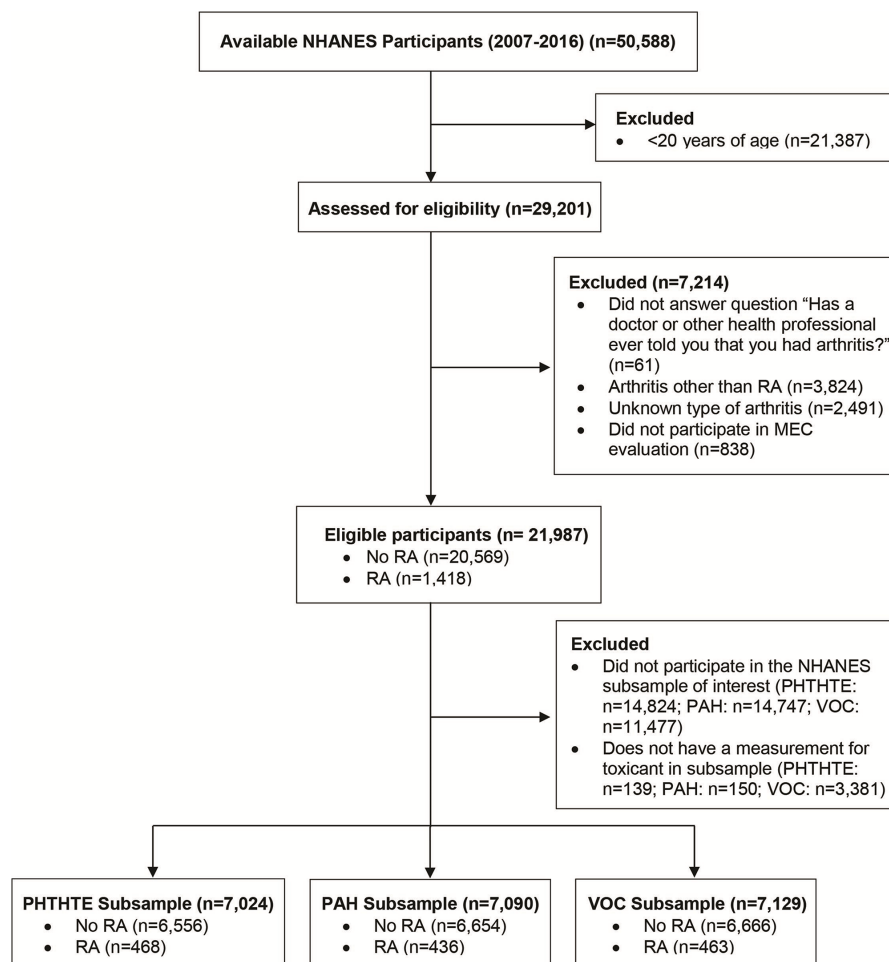
## STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ The current study benefited from the use of National Health and Nutrition Examination Survey (NHANES), a representative data set of the U.S. population which is rich in qualitative and quantitative measures. Specifically, NHANES evaluates a wide variety of toxicants as part of its biospecimen programme along with data related to health, nutrition, behaviours and the environment.
- ⇒ The study explored the association between polycyclic aromatic hydrocarbons (PAHs) (in smokers as well as non-smokers) and rheumatoid arthritis (RA) prevalence while controlling for important confounders.
- ⇒ The study also addressed multicollinearity of toxicants, and performed a mediation analysis to estimate the contributions of smoking and PAHs on RA prevalence.
- ⇒ The limitations of the current study were that the data are cross-sectional and self-reported, and the sample types were limited to blood or urine.

## INTRODUCTION

Rheumatoid arthritis (RA) is an immune-mediated, progressive inflammatory joint disease with many extra-articular features that can lead to irreversible joint damage and decreased quality of life.<sup>1–3</sup> The global age-standardised prevalence of RA is higher in women, increases with age, and peaks between 60 and 64 years of age.<sup>4</sup> North America is consistently one of the highest regions in terms of RA prevalence, reporting a rise of 19% between 1990 and 2017.<sup>4</sup> Therefore, early identification of risk factors is of paramount importance to delay or prevent RA.

While its specific aetiology is partially known, RA is considered a multi-factorial disease that results from interactions between host (eg, sex, age, genetic, etc)<sup>5–7</sup> and environmental (eg, smoking, nutrition, lifestyle, socioeconomic status, etc) risk factors.<sup>8–11</sup> While genetics play a major influence on the development of RA,<sup>12 13</sup>



**Figure 1** Study design. MEC, medical evaluation centre; NHANES, National Health and Nutrition Examination Survey; PAHs, polycyclic aromatic hydrocarbons; PHTHTE, phthalates and plasticisers metabolites; RA, rheumatoid arthritis; VOCs, volatile organic compounds.

other well-established and emerging environmental factors also play a principal role. For example, smoking has the strongest, most-consistent association with RA prevalence.<sup>14</sup> Other factors including body mass index (BMI),<sup>11 15 16</sup> nutrition<sup>17</sup> and alcohol intake<sup>11</sup> are associated with RA prevalence and worse outcomes.

Environmental toxicants which are ubiquitous and can bioaccumulate in human tissue are receiving increasing attention as potential contributors to chronic diseases such as RA. For example, occupational exposure to textile dust, asbestos or noxious airborne agents has been shown to be associated with increased risk of developing RA,<sup>18–22</sup> especially in males with certain occupations.<sup>20 23</sup> In military personnel, exposure to airborne agents from open-air burn pits has been shown to be associated with positivity for RA autoantibodies such as anticyclic citrullinated peptide independent of tobacco use.<sup>24</sup> In addition, heavy metals such as cadmium have been shown to be independently associated with increased RA prevalence<sup>25–27</sup> and have a combined effect with other toxicants on arthritis, especially osteoarthritis.<sup>28</sup>

More specifically, individual toxicants such as polycyclic aromatic hydrocarbons (PAHs), phthalates and

plasticisers (PHTHTEs) and volatile organic compounds (VOCs) have been linked to inflammation and autoimmunity.<sup>29–32</sup> PAHs are a class of ubiquitous chemicals formed from the burning of coal, oil, gas, wood or tobacco, or through the grilling of meat.<sup>33</sup> PHTHTEs are chemicals used in the manufacturing of plastics and are in various consumer products (eg, vinyl flooring, lubricating oils, personal care products, etc).<sup>34</sup> Finally, VOCs are chemicals derived from paints, dry cleaning agents, pharmaceuticals, cleaning supplies, pesticides and building materials.<sup>35</sup> Exposure routes vary, but include the potential consumption, absorption or inhalation of these toxicants.

Emerging evidence suggests that PAHs are associated with increased RA prevalence,<sup>29 30</sup> and that an interaction effect exists between PAHs and smoking.<sup>29</sup> However, it is unclear if PAHs mediate the relationship between smoking and RA prevalence. Moreover, due to the ubiquitous nature of PAHs as well as PHTHTEs and VOCs, it is plausible that all populations, regardless of health behaviours (eg, poor quality diet, smoking, etc), are at risk of developing RA.

**Table 1** Participant characteristics, National Health and Nutrition Examination Survey 2007–1016

Variable	Overall	No rheumatoid arthritis	Rheumatoid arthritis	P value
	Statistics	Statistics	Statistics	
Unweighted, N	21987	20569	1418	
Weighted, N	175972927	167283731	8689197	
Female, % (95% CI)	49.5 (48.9 to 50.2)	48.9 (48.2 to 49.6)	61.8 (58.1 to 65.4)	<b>&lt;0.001*</b>
Age at screening (years), mean (95% CI)	43.8 (43.3 to 44.3)	43.1 (42.6 to 43.6)	57.7 (56.9 to 58.6)	<b>&lt;0.001†</b>
Race, % (95% CI)				
Non-Hispanic white	63.4 (60.0 to 66.8)	63.3 (59.8 to 66.7)	66.0 (61.5 to 70.4)	<b>&lt;0.001*</b>
Non-Hispanic black	12.0 (10.4 to 13.8)	11.7 (10.1 to 13.5)	17.1 (13.9 to 20.7)	
Mexican-American	9.8 (8.0 to 11.8)	9.9 (8.1 to 11.9)	7.4 (5.5 to 9.8)	
Other	14.8 (13.2 to 16.4)	15.1 (13.5 to 16.7)	9.4 (7.4 to 11.7)	
Education level, % (95% CI)‡				
Less than high school	16.7 (15.3 to 18.1)	16.2 (14.8 to 17.6)	25.6 (22.6 to 28.8)	<b>&lt;0.001*</b>
High school/GED/some college/AA	53.1 (51.6 to 54.7)	52.8 (51.2 to 54.3)	59.9 (56.2 to 63.6)	
College graduate+	30.2 (28.1 to 32.3)	31.0 (28.9 to 33.2)	14.5 (11.5 to 17.9)	
Health insurance, % (95% CI)‡				
None	20.8 (19.6 to 22.1)	21.3 (20.0 to 22.7)	11.4 (9.1 to 14.0)	<b>&lt;0.001*</b>
Private	62.1 (60.3 to 63.9)	62.7 (60.8 to 64.6)	49.9 (45.8 to 54.0)	
Other	17.1 (16.0 to 18.2)	16.0 (14.9 to 17.0)	38.7 (35.0 to 42.5)	
Marital status, % (95% CI)				
Married/widowed	57.9 (56.4 to 59.4)	57.5 (56.0 to 59.1)	65.3 (62.2 to 68.3)	<b>&lt;0.001*</b>
Separated/divorced	11.9 (11.2 to 12.6)	11.5 (10.8 to 12.2)	19.5 (17.0 to 22.1)	
Never married/living with partner	30.2 (28.6 to 31.9)	31.0 (29.3 to 32.7)	15.2 (12.9 to 17.8)	
Family PIR, mean (95% CI)‡	2.9 (2.9 to 3.0)	3.0 (2.9 to 3.1)	2.4 (2.3 to 2.6)	<b>&lt;0.001†</b>
Annual household income, % (95% CI)‡				
Under \$55 000	48.7 (46.3 to 51.0)	47.7 (45.4 to 50.1)	66.6 (62.1 to 70.9)	<b>&lt;0.001*</b>
\$55 000–\$99 999	25.5 (24.1 to 26.9)	25.7 (24.3 to 27.1)	22.2 (18.6 to 26.2)	
\$100 000 and up	25.9 (23.5 to 28.3)	26.6 (24.3 to 29.1)	11.2 (8.4 to 14.5)	
Body mass index (kg/m <sup>2</sup> ), mean (95% CI)	28.4 (28.3 to 28.6)	28.3 (28.1 to 28.5)	30.9 (30.4 to 31.5)	<b>&lt;0.001†</b>
Smoking status, % (95% CI)‡				
Never	58.0 (56.7 to 59.4)	58.8 (57.4 to 60.1)	44.2 (40.4 to 48.0)	<b>&lt;0.001*</b>
Past	21.4 (20.4 to 22.5)	20.9 (19.9 to 22.0)	30.4 (26.8 to 34.2)	
Current	20.6 (19.6 to 21.6)	20.3 (19.3 to 21.3)	25.4 (21.9 to 29.3)	
Dietary fibre (gm), mean (95% CI)‡	17.3 (17.1 to 17.6)	17.4 (17.1 to 17.7)	15.5 (14.7 to 16.2)	<b>&lt;0.001†</b>
HEI-2015 score, mean (95% CI)	50.9 (50.5 to 51.3)	51.0 (50.5 to 51.4)	50.3 (49.1 to 51.5)	<b>0.30†</b>
PHQ-9 depression severity, % (95% CI)‡				
None to mild, 0–9	93.3 (92.8 to 93.8)	93.8 (93.3 to 94.3)	83.2 (80.2 to 85.9)	<b>&lt;0.001*</b>
Moderate to severe, 10+	6.7 (6.2 to 7.2)	6.2 (5.7 to 6.7)	16.8 (14.1 to 19.8)	
Any vigorous or moderate activities, % (95% CI)‡	73.8 (72.7 to 74.9)	74.6 (73.5 to 75.7)	58.2 (54.7 to 61.7)	<b>&lt;0.001*</b>
Creatinine, urine (mg/dL), mean (95% CI)‡	123.3 (121.0 to 125.5)	123.7 (121.4 to 126.0)	115.1 (109.5 to 120.8)	<b>0.004*</b>

Bold indicates the significant with  $p < 0.05$ .

\*Rao-Scott  $\chi^2$  test.

†linear regression. MEC weights and SAS SURVEY procedures used for all analyses.

‡Data not available for all subjects. Education level=23; health insurance=22; served in U.S. armed forces=1; marital status=11; family poverty income ratio=1998; annual household income=2020; body mass index (kg/m<sup>2</sup>)=260; smoking status=17; PHQ-9 depression severity=2453; vigorous or moderate activities=9; dietary fibre (gm)=1703; creatinine, urine (mg/dL)=472.

HEI-2015, Healthy Eating Index; PHQ-9, Patient Health Questionnaire-9; PIR, poverty income ratio.

**Table 2** Association between single toxicants and rheumatoid arthritis

Toxicants	Adjustment 1		Adjustment 2	
	OR (95% CI)	P value	OR (95% CI)	P value
<b>PAHs*</b>				
1-hydroxynaphthalene				
Quartile 2 vs 1	1.4 (0.80 to 2.3)	0.25	1.3 (0.76 to 2.3)	0.33
Quartile 3 vs 1	1.8 (1.1 to 2.9)	<b>0.017</b>	1.7 (1.02 to 2.8)	<b>0.040</b>
Quartile 4 vs 1	2.2 (1.4 to 3.5)	<b>&lt;0.001</b>	1.8 (1.1 to 3.1)	<b>0.020</b>
2-hydroxynaphthalene				
Quartile 2 vs 1	1.6 (1.02 to 2.7)	<b>0.043</b>	1.4 (0.90 to 2.3)	0.13
Quartile 3 vs 1	1.7 (1.08 to 2.8)	<b>0.024</b>	1.3 (0.80 to 2.2)	0.27
Quartile 4 vs 1	2.2 (1.4 to 3.4)	<b>&lt;0.001</b>	1.4 (0.86 to 2.4)	0.16
3-hydroxyfluorene				
Quartile 2 vs 1	1.6 (1.1 to 2.2)	<b>0.006</b>	1.5 (1.04 to 2.1)	<b>0.031</b>
Quartile 3 vs 1	1.3 (0.89 to 1.9)	0.17	1.09 (0.71 to 1.7)	0.69
Quartile 4 vs 1	2.2 (1.5 to 3.2)	<b>&lt;0.001</b>	1.4 (0.86 to 2.4)	0.16
2-hydroxyfluorene				
Quartile 2 vs 1	1.6 (1.1 to 2.3)	<b>0.013</b>	1.5 (1.00 to 2.2)	0.050
Quartile 3 vs 1	1.8 (1.2 to 2.7)	<b>0.005</b>	1.5 (0.94 to 2.3)	0.090
Quartile 4 vs 1	2.3 (1.5 to 3.5)	<b>&lt;0.001</b>	1.5 (0.87 to 2.6)	0.14
1-hydroxyphenanthrene				
Quartile 2 vs 1	1.8 (1.2 to 2.8)	<b>0.006</b>	1.7 (1.09 to 2.7)	<b>0.021</b>
Quartile 3 vs 1	1.7 (1.1 to 2.7)	<b>0.017</b>	1.5 (0.92 to 2.3)	0.11
Quartile 4 vs 1	1.8 (1.2 to 3.0)	<b>0.011</b>	1.5 (0.88 to 2.5)	0.14
1-hydroxypyrene				
Quartile 2 vs 1	1.3 (0.92 to 1.8)	0.13	1.2 (0.87 to 1.7)	0.23
Quartile 3 vs 1	1.1 (0.79 to 1.5)	0.56	0.90 (0.61 to 1.3)	0.60
Quartile 4 vs 1	1.8 (1.3 to 2.6)	<b>0.001</b>	1.2 (0.77 to 1.9)	0.41
<b>PHTHTEs†</b>				
Mono(carboxynonyl) phthalate				
Quartile 2 vs 1	0.67 (0.42 to 1.07)	0.096	0.64 (0.38 to 1.09)	0.098
Quartile 3 vs 1	1.04 (0.73 to 1.5)	0.84	1.01 (0.67 to 1.5)	0.96
Quartile 4 vs 1	1.10 (0.72 to 1.7)	0.66	1.02 (0.61 to 1.7)	0.95
Mono(carboxyoctyl) phthalate				
Quartile 2 vs 1	0.97 (0.64 to 1.5)	0.89	0.94 (0.60 to 1.5)	0.78
Quartile 3 vs 1	1.06 (0.73 to 1.5)	0.76	0.99 (0.67 to 1.5)	0.96
Quartile 4 vs 1	1.2 (0.84 to 1.7)	0.32	1.1 (0.78 to 1.6)	0.54
Mono-2-ethyl-5-carboxypentyl phthalate				
Quartile 2 vs 1	1.07 (0.68 to 1.7)	0.77	0.99 (0.63 to 1.6)	0.98
Quartile 3 vs 1	1.2 (0.86 to 1.8)	0.25	1.1 (0.73 to 1.8)	0.55
Quartile 4 vs 1	1.3 (0.86 to 1.9)	0.22	1.09 (0.68 to 1.8)	0.71
Mono-n-butyl phthalate				
Quartile 2 vs 1	1.3 (0.89 to 2.0)	0.15	1.3 (0.81 to 2.0)	0.30
Quartile 3 vs 1	1.2 (0.82 to 1.7)	0.36	1.09 (0.67 to 1.8)	0.73
Quartile 4 vs 1	1.4 (0.97 to 2.0)	0.074	1.2 (0.71 to 2.0)	0.51
Mono-(3-carboxypropyl) phthalate				
Quartile 2 vs 1	0.79 (0.51 to 1.2)	0.31	0.73 (0.46 to 1.2)	0.17
Quartile 3 vs 1	0.87 (0.57 to 1.3)	0.50	0.78 (0.50 to 1.2)	0.26

Continued

Table 2 Continued

Toxicants	Adjustment 1		Adjustment 2	
	OR (95% CI)	P value	OR (95% CI)	P value
Quartile 4 vs 1	1.04 (0.75 to 1.4)	0.80	0.88 (0.61 to 1.3)	0.51
Mono-ethyl phthalate				
Quartile 2 vs 1	1.04 (0.69 to 1.6)	0.85	0.94 (0.62 to 1.4)	0.76
Quartile 3 vs 1	1.08 (0.70 to 1.7)	0.72	0.94 (0.60 to 1.5)	0.78
Quartile 4 vs 1	1.1 (0.75 to 1.6)	0.59	0.88 (0.58 to 1.3)	0.55
Mono-(2-ethyl-5-hydroxyhexyl) phthalate				
Quartile 2 vs 1	1.07 (0.69 to 1.6)	0.77	1.03 (0.64 to 1.6)	0.91
Quartile 3 vs 1	1.5 (1.01 to 2.2)	<b>0.045</b>	1.4 (0.87 to 2.2)	0.170
Quartile 4 vs 1	1.2 (0.82 to 1.9)	0.31	1.09 (0.66 to 1.8)	0.74
Mono-isobutyl phthalate				
Quartile 2 vs 1	1.6 (1.2 to 2.2)	<b>0.002</b>	1.5 (1.05 to 2.1)	<b>0.026</b>
Quartile 3 vs 1	1.2 (0.84 to 1.7)	0.320	1.03 (0.69 to 1.5)	0.88
Quartile 4 vs 1	1.3 (0.87 to 1.9)	0.200	1.01 (0.59 to 1.7)	0.98
Mono-(2-ethyl-5-oxohexyl) phthalate				
Quartile 2 vs 1	1.06 (0.69 to 1.6)	0.80	1.00 (0.64 to 1.6)	0.99
Quartile 3 vs 1	1.3 (0.85 to 1.9)	0.25	1.2 (0.73 to 1.8)	0.52
Quartile 4 vs 1	1.3 (0.86 to 1.9)	0.23	1.07 (0.69 to 1.7)	0.75
Mono-benzyl phthalate				
Quartile 2 vs 1	1.6 (1.01 to 2.5)	<b>0.043</b>	1.5 (0.92 to 2.4)	0.11
Quartile 3 vs 1	1.3 (0.93 to 1.9)	0.120	1.09 (0.72 to 1.7)	0.67
Quartile 4 vs 1	1.9 (1.3 to 2.9)	<b>0.002</b>	1.5 (0.87 to 2.6)	0.140
<b>VOCs‡</b>				
Toluene				
Quartile 2 vs 1	1.03 (0.72 to 1.5)	0.89	1.1 (0.58 to 2.1)	0.72
Quartile 3 vs 1	1.10 (0.76 to 1.6)	0.62	1.09 (0.68 to 1.7)	0.7
Quartile 4 vs 1	1.7 (1.1 to 2.5)	<b>0.009</b>	1.09 (0.69 to 1.7)	0.7

Toxicant subsets and corresponding subsample weights were used.

Adjustment 1: adjusted for age and sex (male vs female).

Adjustment 2: adjusted for age, sex (male vs female), body mass index, urine creatinine, smoking (never vs past vs current), race (non-Hispanic white vs non-Hispanic black vs Mexican-American vs other), education (high school or less vs more than high school), family poverty income ratio, any vigorous or moderate activity (yes vs no) and dietary fibre.

All models were fitted on each of the five imputed datasets and parameter estimates were combined using SAS MIANALYZE.

Bold indicates the significant with  $p < 0.05$ .

\*PAH subset (n=7090) and corresponding subsample weights used.

†PHT subset (n=7024) and corresponding subsample weights used.

‡VOC subset (n=7129) and corresponding subsample weights used.

PAHs, polycyclic aromatic hydrocarbons; PHTHTEs, phthalates and plasticisers metabolites; VOCs, volatile organic compounds.

Therefore, the objective of the current study was to examine the associations between various environmental toxicants and RA among U.S. adults while adjusting for other non-heritable risk factors of RA.

## METHODS

### Study design and population

A cross-sectional analysis was conducted with adult participants using data collected between 2007 and 2016 of the National Health and Nutrition Examination Survey (NHANES), a national survey that evaluates the health

and nutritional status of adults and children in the U.S.<sup>36</sup> NHANES combines interviews and physical examinations for participants, and the sample is selected to represent the U.S. population.<sup>36</sup> All participants provided informed consent. The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for cross-sectional studies.<sup>37</sup>

Figure 1 summarises the study design. The study population included adults who participated in health interviews conducted in their homes and health evaluations conducted in regional mobile examination centres

**Table 3** Association between single PAH and PHTHTE body burden scores and rheumatoid arthritis

Variable	Adjustment 1		Adjustment 2	
	OR (95% CI)	P value	OR (95% CI)	P value
PAH body burden*				
Quartile 2 vs 1	1.5 (0.91 to 2.4)	0.11	1.5 (0.87 to 2.5)	0.15
Quartile 3 vs 1	1.9 (1.2 to 3.1)	<b>0.012</b>	1.7 (0.97 to 3.0)	0.066
Quartile 4 vs 1	2.6 (1.5 to 4.4)	<b>&lt;0.001</b>	2.2 (1.09 to 4.2)	<b>0.028</b>
PHTHTE body burden†				
Quartile 2 vs 1	1.6 (1.00 to 2.6)	0.052	1.6 (0.91 to 2.6)	0.10
Quartile 3 vs 1	1.6 (0.99 to 2.5)	0.056	1.4 (0.82 to 2.4)	0.21
Quartile 4 vs 1	1.8 (1.06 to 2.9)	<b>0.030</b>	1.6 (0.89 to 2.8)	0.12

PHTHTE body burden score includes: mono-2-ethyl-5-carboxypentyl phthalate, mono-n-butyl phthalate, mono-ethyl phthalate, mono-(2-ethyl-5-hydroxyhexyl) phthalate, mono-isobutyl phthalate, mono-(2-ethyl-5-oxohexyl) phthalate, mono-benzyl phthalate, mono(carboxynonyl) phthalate, mono(carboxyoctyl) phthalate and mono-(3-carboxypropyl) phthalate.

Adjustment 1: adjusted for age and sex (male vs female).

Adjustment 2: adjusted for age, sex (male vs female), body mass index, urine creatinine, smoking (never vs past vs current), race (non-Hispanic white vs non-Hispanic black vs Mexican-American vs other), education (high school or less vs more than high school), family poverty income ratio, any vigorous or moderate activity (yes vs no) and dietary fibre.

All models were fitted on each of the five imputed datasets and parameter estimates were combined using SAS MIANALYZE.

Bold indicates the significant with  $p < 0.05$ .

\*PAH subset (n=7090) with PAH subsample weights used for analysis. PAH body burden score includes: 1-hydroxynaphthalene, 2-hydroxynaphthalene, 3-hydroxyfluorene, 2-hydroxyfluorene, 1-hydroxyphenanthrene and 1-hydroxypyrene.

†PHTHTE subset (n=7024) with PHTHTE subsample weights used for analysis.

PAH, polycyclic aromatic hydrocarbons; PIR, poverty income ratio.

(MECs). The RA group included adult participants who answered 'Yes' to 'Has a doctor or other health professional ever told you that you had arthritis?' and answered 'Rheumatoid Arthritis' to 'Which type of arthritis was it?'. The control group (no RA) is made up of those who answered 'No' to 'Has a doctor or other health professional ever told you that you had arthritis?'.

### Data availability and collection

All demographic data were collected as part of health interviews conducted in participants' homes. Health-related measurements and biospecimens were collected at MECs. Biospecimens were stored and analysed as described.<sup>38–40</sup> Data were accessed and downloaded from the NHANES laboratory data files. Toxicants and their metabolites were evaluated if >85% of samples were over the lower limit of detection across all survey years (30 of 38 toxicant metabolites; online supplemental table 1), if they are fat-soluble (or persistent within the body) or have a previous association with RA. Based on these criteria, we selected the following toxicants and their metabolites: PAHs (urine), PHTHTEs (urine) and VOCs (blood). Toxicant combined cycle sampling weights were constructed following NHANES guidelines.<sup>41</sup>

Eligible participants were organised into three subsample groups (PAH, PHTHTE and VOC). To be included in a group, a participant needed to have participated in the NHANES subsample of interest (subsample weight >0) and have at least one, measured toxicant metabolite from that group of interest (online supplemental table

2). The VOC subsample included only toluene as the other metabolites were below the lower limit of detection.

### Statistical analysis

Analyses were performed according to published NHANES analytic guidelines<sup>41</sup> using the SURVEY procedures in SAS V.9.4 (SAS Institute). Continuous measures were summarised using weighted means and SEs, or medians and IQRs, and were compared between subjects without RA and those with RA using t-tests or linear regression on logged values. Categorical factors were summarised using weighted percentages and SEs and were compared using Rao-Scott  $\chi^2$  tests. Reliability of the descriptive estimates was evaluated by the relative SE for means and using the National Center for Health Statistics' guidelines for proportions.<sup>42</sup> PAH, PHTHTE and VOC combined cycle sampling weights were constructed following NHANES guidelines.<sup>41</sup>

Associations between individual toxicants and RA were assessed using multivariable logistic regression with RA modelled as the outcome. For this, individual toxicants were divided into quartiles. Variables were selected based on inclusion in previous studies, clinical importance and statistical importance following univariate analysis and included age, sex (male vs female), urine creatinine,<sup>38 43</sup> BMI, smoking (never vs past vs current), race (non-Hispanic white vs non-Hispanic black vs Mexican-American vs other), education (high school or less vs more than high school), family poverty income ratio (PIR), any vigorous or moderate activity (yes vs no) and

**Table 4** Mediation analysis to evaluate the effects of PAH body burden on the relationship between smoking and rheumatoid arthritis

	PAH subset
Indirect effect* of current smoking mediated by PAH	0.7626
Indirect effect of past smoking mediated by PAH	0.0684
Total indirect (mediated) effect of smoking	0.831
Direct effect of current smoking	0.0874
Direct effect of past smoking	0.0168
Total direct effect of smoking	0.1042
Total effect† of current smoking	0.8499
Total effect of past smoking	0.0852
Total effect of smoking	0.9352
Percent of total effect (current smoking) mediated‡	89.72
Percent of total effect (past smoking) mediated	80.28
Percent of total effect mediated	88.86

PAH subset (n=7090) with PAH subsample weights used for analysis. Adjustment includes age, sex (male vs female), race (non-Hispanic white vs non-Hispanic black vs Mexican-American vs other), education (high school or less vs more than high school), family poverty income ratio, smoking (never vs past vs current), body mass index, urine creatinine, any vigorous or moderate activity (yes vs no) and dietary fibre.

\*The effects are obtained from the linear predictors (log(OR)) of logistic regression models and represent a measure of association where positive values mean the variable increases the likelihood of the outcome.

†Total effect=direct+indirect effect.

‡Percent of total effect mediated=100\*(indirect/total).

PAHs, polycyclic aromatic hydrocarbons.

dietary fibre. A lower PIR indicates higher poverty. Two adjustments were performed: adjustment 1 included age and sex, and adjustment 2 (fully adjusted model) included age, sex (male vs female), BMI (kg/m<sup>2</sup>), urine creatinine (mg/dL), smoking (never vs past vs current), race (non-Hispanic white vs non-Hispanic black vs Mexican-American vs other), education (high school or less vs more than high school), family PIR, any vigorous or moderate activity (yes vs no) and dietary fibre (g).

A body burden score was also established for PAHs and PHTHTEs and represented the total amount of metabolites detected in the body in each of these toxicant classes at the time of measurement. Rank-based correlations between the individual metabolites were assessed to avoid the potential for multicollinearity using the %Survey-CorrCov macro (online supplemental etable 3),<sup>44</sup> and then clustering analyses were performed as described previously.<sup>44</sup> Standardised scoring coefficients obtained from the clustering analysis were used to calculate a weighted body burden for the PAH and PHTHTE subsamples. Body burden scores for PAHs and PHTHTEs were divided into quartiles and used in multivariable logistic regression analyses with the adjustments described above. Body burden scores were not established for the VOC subsample as only a single toxicant was analysed.

Bayesian bootstrap was used to impute five datasets with complete data using SAS SURVEYIMPUTE. The multiple imputation included all of the aforementioned variables. All models were fitted on each of the five imputed datasets and parameter estimates were combined using SAS MIANALYZE.

### Environmental toxicants and smoking

A mediation analysis was performed to explore if PAH body burden lies within the causal pathway between smoking and RA. Before proceeding with the analysis, three criteria were assessed to ensure mediation can be established as described previously.<sup>45</sup> Multivariable logistic regression analyses were then performed with the aforementioned adjustments. The mediation analysis was summarised into direct and indirect effects mediated by PAH body burden. The effects presented are obtained from the linear predictors (log(OR)) and represent a measure of association where positive values mean the variable increases the likelihood of the outcome. The percent of total effect mediated by PAH body burden is calculated from these effects values to appreciate the proportion of direct and indirect effects mediated by PAH body burden.

### Additional analyses

Two additional analyses were performed. The first compared the participants who were and were not included in the study (online supplemental etable 4). The second examined the association between PAH body burden and RA among never smokers. All tests were two-tailed and performed at a significance level of 0.05.

### PATIENTS AND PUBLIC INVOLVEMENT

No patient or public involvement in the current study.

### RESULTS

The eligible study population included 21 987 adults (control: 20 569; RA: 1418) (figure 1). PAHs were measured in 7090 participants (no RA: 6654; RA: 436), PHTHTEs were measured in 7024 (no RA: 6556; RA: 468) and VOCs were measured in 7129 participants (no RA: 6666; RA: 463). These subsamples were not exclusive with 4243 participants having both PAHs and PHTHTEs measured (286 of which had RA), and 3133 participants having both PAHs and VOCs measured (178 of which had RA). There were no substantial differences between participants included versus excluded from the study (online supplemental etable 4).

Participant characteristics are summarised in table 1. Participants with self-reported RA were more likely to be women, older, non-Hispanic black and to have an annual household income of under \$55 000 (p<0.001). Participants with self-reported RA were also less likely to be a college graduate and had a lower PIR and were more likely to be a past or current smoker, have an elevated

BMI, participate in less physical activity and consume less dietary fibre ( $p<0.001$ ). However, the mean Healthy Eating Index (HEI-2015) scores between each group were similar ( $p=0.30$ ) suggesting similar diet quality. Further examination of the radar plots for the HEI-2015 score confirmed that the diet quality among food domains was similar between groups (online supplemental figure 1).

**Table 2** summarises the association of individual toxicants with RA. Increased prevalence of RA was observed in participants with the highest quartile of various PAHs including 1-hydroxynaphthalene (OR: 2.2 (95% CI 1.4 to 3.5);  $p<0.001$ ), 2-hydroxynaphthalene (OR: 2.2 (1.4 to 3.4);  $p<0.001$ ), 3-hydroxyfluorene (OR: 2.2 (1.5 to 3.2);  $p<0.001$ ), 2-hydroxyfluorene (OR: 2.3 (1.5 to 3.5);  $p<0.001$ ), 1-hydroxyphenanthrene (OR: 1.8 (1.2 to 3.0);  $p=0.011$ ) and 1-hydroxypyrene (OR: 1.8 (1.3 to 2.6);  $p=0.001$ ). Most, but not all, exhibited a dose-dependency with RA. In the fully adjusted model, however, the only toxicant that remained associated with RA in participants with the highest quartile was 1-hydroxynaphthalene (OR: 1.8 (1.1 to 3.1);  $p=0.020$ ).

Increased RA was only observed in participants with the highest quartile of one PHTHTE, mono-benzyl phthalate (OR: 1.9 (1.3 to 2.9);  $p=0.002$ ). However, the lowest quartile was also associated with increased RA, though this relationship was not as strong (OR: 1.6 (1.01 to 2.5);  $p=0.043$ ). These relationships were attenuated in the fully adjusted model. Other PHTHTEs demonstrated associations with increased RA, but at lower quartiles and did not exhibit a monotonic trend. Similarly, the observed relationships were mostly attenuated in the fully adjusted model. Increased RA was observed in participants with the highest quartile of the VOC, toluene (OR: 1.7 (1.1 to 2.5);  $p=0.009$ ); however, this relationship was attenuated in the fully adjusted model.

The association of PAH and PHTHTE body burden with RA were then examined (**table 3**). PAH body burden demonstrated a monotonic relationship with RA with those in the highest quartile exhibiting the greatest risk (OR: 2.6 (1.5 to 4.4);  $p<0.001$ ). In the fully adjusted model, increased RA remained dose-dependently related to PAH body burden (OR: 2.2 (1.09 to 4.2);  $p=0.028$ ). PHTHTE body burden was also associated with RA with those in the highest quartile exhibiting the greatest risk (OR: 1.8 (1.06 to 2.9);  $p=0.03$ ); however, this relationship was attenuated in the fully adjusted model.

Additionally, the association of PAH body burden with RA remained significant even with the stepwise addition of urine creatinine, BMI, smoking and race (OR: 2.2 (1.09 to 4.2);  $p=0.028$ ) (online supplemental eTable 5). Interestingly, when accounting for PAH body burden, smoking was not significantly associated with RA (OR: 1.4 (0.89 to 2.3);  $p=0.13$ ).

In light of these findings, and because smoking is associated with an elevated risk for RA<sup>8</sup> and cigarettes are a known source of PAHs,<sup>33</sup> a mediation analysis was performed to determine if PAH body burden mediates the relationship between smoking and RA. PAH body

burden met the criteria for mediation (online supplemental eTable 6). Specifically, smoking was associated with RA (OR: 1.7 (1.3 to 2.3);  $p<0.001$ ), smoking was associated with PAH body burden (OR: 87.2 (43.9 to 172.8);  $p<0.001$ ) and PAH body burden was associated with RA after adjusting for smoking (OR: 2.2 (1.09 to 4.2);  $p=0.028$ ). **Table 4** summarises the mediation analysis. PAH body burden mediated almost 90% of the total effect of smoking on RA.

Additionally, PAH body burden was also significantly and monotonically associated with RA in non-smokers (online supplemental eTable 7; OR: 3.0 (1.3 to 7.1);  $p=0.013$ ). However, despite a similar trend in the fully adjusted model, it did not achieve significance (OR: 2.5 (0.86 to 7.1);  $p=0.092$ ).

## DISCUSSION

While it is evident that various toxicants exist within the bodies of residents of the U.S.,<sup>46</sup> research is now mounting to demonstrate their association with various chronic conditions. However, there is a paucity of studies linking environmental toxicants with chronic inflammatory conditions such as RA. The current study confirms and, more importantly, expands the limited, evidence for the relationship between PAHs and RA. The current study reports three important findings. First, PAHs are significantly associated with RA. Second, PAHs largely mediate the relationship between smoking and RA. Third, PAHs are present in non-smokers and are significantly associated with RA. To our knowledge, this is the first study to demonstrate that environmental exposure to PAHs mediate the majority of the association between smoking and RA, and also contribute to population burden of RA independently of smoking status.

To date, few studies have examined the relationship between PAHs and RA and findings are mixed. Using NHANES data, Sun and colleagues<sup>29</sup> evaluated various individual PAHs and demonstrated that the majority were associated with RA in a model adjusted for age and sex, but only a subset were significantly associated with RA in a fully adjusted model. They also found that participants with higher PAH scores did not have a higher propensity for RA. However, when they accounted for smoking status, those who were current smokers had a higher prevalence of RA which was substantially increased in the setting of high PAH scores. Similarly, Li and colleagues<sup>30</sup> reported a significant relationship between PAHs grouped by highest quartile and RA in an unadjusted model; however, the relationship was attenuated in fully adjusted model that included age, sex, BMI, PIR alcohol consumption, subsampling weighting smoking status.

There are several potential reasons for this discrepancy. Previous studies used different NHANES cycles which can capture temporal changes in toxicant exposures<sup>47</sup> and societal behavioural changes (eg, less smoking). Additionally, Li and colleagues dichotomised their PAH body burden (participants <median or  $\geq$ median) which may have



muted potential effects in more precise analyses between quartiles. Their use of multiple imputation methods may not have accurately accounted for missing data. Most importantly, the current study adjusted for nutrition and lifestyle-related covariates in stepwise fashion. These covariates were added to the models as fibre<sup>48</sup> and exercise (especially with sweating),<sup>49 50</sup> which can support the biotransformation and elimination of toxicants from the body. Yang and colleagues<sup>51</sup> recently used NHANES data to highlight the importance of healthy nutrition and lifestyle behaviours, especially for women, in the setting of elevated PAH levels. Using a lifestyle index that accounted for alcohol consumption, smoking, BMI, physical activity and diet, they demonstrated that, in the setting of high PAH levels, females who followed healthy nutrition and lifestyle-related behaviours experienced less phenotypic ageing, and subsequently less inflammatory burden that could potentially result in chronic disease. Therefore, healthy nutrition and lifestyle-related behaviours may be especially important for women as they are at higher risk for RA and carry more adipose tissue which can sequester toxicants.<sup>50</sup> Such behaviours can facilitate the biotransformation and elimination of toxicants from the body thereby avoiding potential epigenetic alterations that could contribute to the manifestation of RA.

To our knowledge, this is the first study to demonstrate that PAHs not only underlie the majority of the relationship between smoking and RA, but also independently contribute to RA. This is important as PAHs are ubiquitous in the environment, derived from various sources and are mechanistically linked by the aryl hydrocarbon receptor to the underlying pathophysiology of RA.<sup>52</sup> While PAH levels tend to be higher in adults who smoke, they are also found in most U.S. residents.<sup>29</sup> Other sources of PAH exposure include indoor environments,<sup>33 53</sup> motor vehicle exhaust, natural gas, smoke from wood or coal burning fires, fumes from asphalt roads and consuming grilled or charred foods.<sup>33</sup> This is pertinent as households of lower socioeconomic status generally experience poorer indoor air quality and may reside in urban areas next to major roadways or in high traffic areas.<sup>54 55</sup> In the absence of healthy nutrition and lifestyle behaviours, populations of lower socioeconomic status may also be at greater risk of chronic conditions such as RA due to environmental toxicant exposures.

### Limitations

First, since NHANES provides cross-sectional data, we cannot rule out the possibility that the environmental toxicant exposures presented here may not predate the development of RA. However, it is recognised that many toxicant exposures do not occur as isolated events, and that individuals are continually accumulating toxicants.<sup>46</sup> Second, since NHANES relies on participants self-reporting their RA diagnosis, there is a plausibility of over reporting. However, to the extent that our outcome was diluted with patients who do not have RA, our estimates of the association with PAH would be underestimated.

Third, the study is limited by the available sample types within NHANES (blood or urine) to measure environmental toxicant levels. While both sample types provide an estimation of biological levels, they may also be underestimating body burden especially if exposure is continuous.<sup>49</sup> The best estimate of body burden would be to also assess toxicant levels in adipose tissue in addition to blood and urine; however, this sample type is not currently available. Fourth, the authors cannot rule out the potential for selection bias in the toxicant subsamples, and differences exist in specific characteristics for those excluded versus included in the subsamples (eg, creatinine). Fifth, although the current study evaluated body burden, we did not statistically account for multiple toxicant classes which may be more representative of human exposure.<sup>56</sup> Sixth, previous research has demonstrated that heavy metals, such as cadmium, are associated with increased prevalence of RA.<sup>26</sup> While the current study did not examine heavy metals, the authors recognise cigarettes as a major source of cadmium which can have a major effect on RA development. Finally, the authors made many comparisons so the study is considered exploratory vs hypothesis testing. Therefore, findings should not be considered definitive and should be replicated in other data sets.

### CONCLUSION

The current study supports and expands the available evidence demonstrating that environmental PAHs are associated with RA prevalence in the U.S. population, regardless of smoking status. Future studies would evaluate the mechanisms underlying the aetiology of RA while taking into consideration the interaction between environmental toxicants such as PAHs and heavy metals, and examine the relationship between socioeconomic status, PAHs and RA.

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eTable 1. Individual toxicants by NHANES Cycle (2007-2016)

Toxicant	All (2007-2016)		2007-2008		2009-2010		2011-2012		2013-2014		2015-2016	
	N missing	Statistics	N missing	Statistics	N missing	Statistics	N missing	Statistics	N missing	Statistics	N missing	Statistics
<b>PAHs*</b>												
Unweighted N		7,090		1,390		1,510		1,354		1,414		1,422
Weighted N		173,544,330		33,185,220		34,708,969		35,108,975		34,911,478		35,629,688
1-hydroxynaphthalene (ng/L), median [Q1, Q3]	130	1558.7 [651.8, 5309.9]	57	2223.5 [901.3, 8247.8]	0	1830.8 [757.7, 5640.7]	0	1597.2 [636.2, 4970.6]	7	1249.1 [537.4, 3869.7]	66	1271.1 [542.1, 3893.9]
2-hydroxynaphthalene (ng/L), median [Q1, Q3]	62	4225.5 [1868.4, 10121.4]	33	3891.4 [1877.6, 9396.9]	0	3522.7 [1569.8, 8250.6]	0	4436.5 [1906.4, 10645.0]	4	4237.6 [1770.6, 10310.5]	25	5262.7 [2274.6, 11616.5]
3-hydroxyfluorene (ng/L), median [Q1, Q3]	25	79.7 [38.7, 226.8]	15	97.7 [48.5, 342.2]	2	78.5 [39.0, 217.6]	4	78.4 [40.3, 225.2]	0	68.6 [31.4, 194.6]	4	74.3 [32.0, 198.1]
2-hydroxyfluorene (ng/L), median [Q1, Q3]	11	213.8 [101.9, 524.5]	11	280.0 [143.8, 796.0]	0	221.3 [107.3, 539.5]	0	227.6 [110.4, 585.2]	0	159.6 [80.5, 416.6]	0	181.8 [84.1, 413.5]
3-hydroxyphenanthrene (ng/L), median [Q1, Q3]	2842	75.9 [38.0, 154.2]	5	103.2 [53.5, 190.3]	1	70.5 [35.5, 133.0]	0	63.0 [30.5, 134.1]	1414	---	1422	---
1-hydroxyphenanthrene (ng/L), median [Q1, Q3]	1	122.8 [64.8, 225.8]	0	145.7 [80.9, 259.7]	1	140.5 [72.8, 239.3]	0	131.3 [70.5, 252.2]	0	95.6 [52.1, 178.8]	0	102.6 [56.7, 195.1]
2-hydroxyphenanthrene (ng/L), median [Q1, Q3]	2855	67.0 [36.4, 124.0]	17	69.4 [38.0, 128.2]	1	68.1 [36.2, 120.3]	1	64.1 [34.2, 124.2]	1414	---	1422	---
1-hydroxypyrene (ng/L), median [Q1, Q3]	25	114.7 [50.0, 224.6]	22	123.3 [58.6, 234.7]	0	114.7 [53.5, 225.6]	2	109.9 [53.6, 215.7]	0	115.3 [49.5, 222.5]	1	107.8 [49.5, 208.5]
9-hydroxyfluorene (ng/L), median [Q1, Q3]	2836	294.2 [139.2, 610.9]	0	364.4 [177.8, 716.9]	0	266.6 [128.5, 552.9]	0	266.0 [119.9, 546.9]	1414	---	1422	---
<b>PHTHTEs†</b>												
Unweighted N		7,024		1,386		1,511		1,352		1,425		1,350
Weighted N		174,032,721		33,073,405		34,766,079		35,067,724		35,244,749		35,880,763
Mono(carboxynonyl) Phthalate (ng/mL), median [Q1, Q3]	0	2.3 [1.2, 4.6]	0	2.2 [1.2, 4.4]	0	2.8 [1.4, 5.7]	0	2.3 [1.1, 4.7]	0	2.5 [1.3, 5.4]	0	1.6 [0.78, 3.0]
Mono(carboxyoctyl) Phthalate (ng/mL), median [Q1, Q3]	0	10.4 [4.3, 31.3]	0	6.0 [2.9, 13.6]	0	11.1 [4.4, 31.9]	0	18.2 [6.8, 52.9]	0	18.0 [7.4, 53.5]	0	6.7 [3.2, 16.5]
Mono-2-ethyl-5-carboxypentyl phthalate (ng/mL), median [Q1, Q3]	0	13.7 [6.5, 28.2]	0	29.8 [14.7, 62.2]	0	18.9 [9.5, 38.6]	0	12.9 [6.3, 24.5]	0	10.1 [5.0, 18.2]	0	8.4 [4.0, 16.1]

Mono-n-butyl phthalate (ng/mL), median [Q1, Q3]	0	12.0 [5.5, 23.5]	0	18.8 [9.4, 34.5]	0	14.9 [7.0, 28.6]	0	8.5 [3.4, 19.2]	0	9.4 [4.2, 18.0]	0	10.0 [5.3, 18.4]
Mono-(3-carboxypropyl) phthalate (ng/mL), median [Q1, Q3]	0	2.1 [0.89, 4.9]	0	2.4 [1.2, 5.0]	0	2.9 [1.3, 6.0]	0	2.6 [1.2, 6.5]	0	1.8 [0.75, 4.8]	0	0.91 [0.32, 2.0]
Mono-ethyl phthalate (ng/mL), median [Q1, Q3]	0	44.5 [16.5, 137.9]	0	87.2 [34.1, 268.4]	0	62.5 [23.0, 189.5]	0	33.3 [13.3, 107.6]	0	31.4 [12.6, 86.8]	0	28.4 [11.7, 89.5]
Mono-(2-ethyl-5-oxohexyl) phthalate (ng/mL), median [Q1, Q3]	0	5.5 [2.6, 11.4]	0	10.7 [5.2, 25.4]	0	7.7 [3.6, 15.3]	0	5.0 [2.5, 9.7]	0	4.3 [1.9, 7.6]	0	3.4 [1.6, 6.7]
Mono-benzyl phthalate (ng/mL), median [Q1, Q3]	0	4.8 [2.0, 11.5]	0	7.2 [3.1, 16.0]	0	6.1 [2.6, 13.2]	0	3.9 [1.8, 9.8]	0	4.1 [1.7, 9.2]	0	3.9 [1.6, 8.9]
<b>VOCs<sup>‡</sup></b>												
Unweighted N		7,090		1,390		1,510		1,354		1,414		1,422
Weighted N		173,544,330		33,185,220		34,708,969		35,108,975		34,911,478		35,629,688
Toluene (ng/mL), median [Q1, Q3]	2851	0.07 [0.05, 0.17]	181	0.09 [0.05, 0.22]	772	0.07 [0.04, 0.18]	1818	---	71	0.07 [0.05, 0.14]	9	0.07 [0.05, 0.15]

-- : Not available

\*PAH subset (n = 7,090) and corresponding subsample weights used

† PHT subset (n = 7,024) and corresponding subsample weights used

‡VOC subset (n = 7,129) and corresponding subsample weights used

SAS Survey Procedures used for all analyses.

eTable 2. Individual toxicants by group, NHANES 2007-2016

Toxicant	No Rheumatoid Arthritis		Rheumatoid Arthritis		p-value
	N Missing	Statistics	N Missing	Statistics	
<b>PAHs*</b>					
Unweighted N		6,654		436	---
Weighted N		165,527,760		8,016,570	---
1-hydroxynaphthalene (ng/L), median [Q1, Q3]	113	1526.8 [644.1, 5152.0]	17	2364.6 [784.5, 8555.8]	<b>&lt;0.001<sup>b</sup></b>
2-hydroxynaphthalene (ng/L), median [Q1, Q3]	50	4222.2 [1852.4, 10052.7]	12	4300.3 [2126.1, 10533.7]	0.10 <sup>b</sup>
3-hydroxyfluorene (ng/L), median [Q1, Q3]	23	79.8 [38.0, 225.3]	2	75.2 [39.8, 268.5]	0.38 <sup>b</sup>
2-hydroxyfluorene (ng/L), median [Q1, Q3]	9	213.5 [101.7, 523.6]	2	226.0 [118.7, 608.6]	0.17 <sup>b</sup>
3-hydroxyphenanthrene (ng/L), median [Q1, Q3]	2695	76.0 [38.0, 154.3]	147	71.0 [37.9, 152.8]	0.75 <sup>b</sup>
1-hydroxyphenanthrene (ng/L), median [Q1, Q3]	1	122.6 [64.0, 225.9]	0	122.9 [73.7, 222.3]	0.63 <sup>b</sup>
2-hydroxyphenanthrene (ng/L), median [Q1, Q3]	2705	67.7 [36.4, 124.0]	150	61.9 [36.7, 111.9]	0.79 <sup>b</sup>
1-hydroxypyrene (ng/L), median [Q1, Q3]	20	115.9 [51.0, 225.7]	5	105.1 [49.4, 209.0]	0.22 <sup>b</sup>
9-hydroxyfluorene (ng/L), median [Q1, Q3]	2690	291.2 [138.6, 604.5]	146	336.9 [160.6, 659.2]	0.095 <sup>b</sup>
<b>PHTHTEs†</b>					
Unweighted N		6,556		468	---
Weighted N		165,218,598		8,814,123	---
Mono(carboxynonyl) Phthalate (ng/mL), median [Q1, Q3]	0	2.3 [1.2, 4.6]	0	2.2 [1.00, 4.3]	0.2 <sup>b</sup>
Mono(carboxyoctyl) Phthalate (ng/mL), median [Q1, Q3]	0	10.5 [4.3, 31.3]	0	9.4 [4.2, 28.1]	0.52 <sup>b</sup>
Mono-2-ethyl-5-carboxypentyl phthalate (ng/mL), median [Q1, Q3]	0	13.7 [6.5, 28.2]	0	14.1 [6.5, 27.7]	0.75 <sup>b</sup>
Mono-n-butyl phthalate (ng/mL), median [Q1, Q3]	0	12.0 [5.5, 23.4]	0	12.3 [6.5, 24.3]	0.17 <sup>b</sup>
Mono-(3-carboxypropyl) phthalate (ng/mL), median [Q1, Q3]	0	2.1 [0.89, 4.8]	0	1.9 [0.76, 5.2]	0.76 <sup>b</sup>
Mono-ethyl phthalate (ng/mL), median [Q1, Q3]	0	44.2 [16.5, 137.6]	0	48.3 [17.5, 143.9]	0.28 <sup>b</sup>
Mono-(2-ethyl-5-oxohexyl) phthalate (ng/mL), median [Q1, Q3]	0	8.9 [4.0, 18.7]	0	9.2 [4.0, 16.8]	0.52 <sup>b</sup>
Mono-benzyl phthalate (ng/mL), median [Q1, Q3]	0	7.5 [3.5, 14.4]	0	6.8 [3.5, 12.9]	0.43 <sup>b</sup>
<b>VOCs‡</b>					
Unweighted N		9,348		632	---
Weighted N		159,508,473		8,249,605	---
Toluene (ng/mL), median [Q1, Q3]	2682	0.07 [0.05, 0.17]	169	0.08 [0.05, 0.24]	0.092 <sup>b</sup>

**Bold** = Significant with  $p < 0.05$

---: Not available

Abbreviations: Polycyclic Aromatic Hydrocarbons: PAHs; PHTHTEs: Phthalates and Plasticizers Metabolites; VOCs: Volatile Organic Compounds

\*PAH subset (n = 7,090) and corresponding subsample weights used

† PHT subset (n = 7,024) and corresponding subsample weights used

‡VOC subset (n = 7,129) and corresponding subsample weights used

P-values: b=linear regression with log transformation; c=Rao-Scott chi-square test.

SAS Survey Procedures used for all analyses.

**eTable 3. Rank-based correlations between single PAH (a) and PHTHTE (b) toxicants****a.**

PAH concentration (ng/L)	1-hydroxynaphthalene	2-hydroxynaphthalene	3-hydroxyfluorene	2-hydroxyfluorene	1-hydroxyphenanthrene	1-hydroxypyrene
1-hydroxynaphthalene	1.0000	0.5865	0.7300	0.7200	0.5910	0.5770
2-hydroxynaphthalene	0.5865	1.0000	0.6628	0.6860	0.5679	0.6235
3-hydroxyfluorene	0.7300	0.6628	1.0000	0.9565	0.7375	0.7754
2-hydroxyfluorene	0.7200	0.6860	0.9565	1.0000	0.7920	0.7871
1-hydroxyphenanthrene	0.5910	0.5679	0.7375	0.7920	1.0000	0.7958
1-hydroxypyrene	0.5770	0.6235	0.7754	0.7871	0.7958	1.0000

Abbreviations: Polycyclic Aromatic Hydrocarbons: PAHs  
PAH subsample weights used

**b.**

PHTHTE concentration (ng/mL)	Mono(carboxynonyl) phthalate	Mono(carboxyoctyl) phthalate	Mono-2-ethyl-5-carboxypentyl phthalate	Mono-n-butyl phthalate	Mono-(3-carboxypropyl) phthalate	Mono-ethyl phthalate	Mono-(2-ethyl-5-hydroxyhexyl) phthalate	Mono-isobutyl phthalate	Mono-(2-ethyl-5-oxohexyl) phthalate	Mono-benzyl phthalate
Mono(carboxynonyl) phthalate	1.0000	0.6694	0.5236	0.4093	0.6655	0.2755	0.4667	0.4057	0.4850	0.3850
Mono(carboxyoctyl) phthalate	0.6694	1.0000	0.4186	0.3035	0.7215	0.1702	0.3650	0.3619	0.3922	0.2986
Mono-2-ethyl-5-carboxypentyl phthalate	0.5236	0.4186	1.0000	0.6302	0.6183	0.3959	0.9343	0.5337	0.9416	0.5224
Mono-n-butyl phthalate	0.4093	0.3035	0.6302	1.0000	0.5338	0.4632	0.6533	0.7551	0.6673	0.6875
Mono-(3-carboxypropyl) phthalate	0.6655	0.7215	0.6183	0.5338	1.0000	0.3092	0.5891	0.4467	0.6081	0.4682
Mono-ethyl phthalate	0.2755	0.1702	0.3959	0.4632	0.3092	1.0000	0.3988	0.4076	0.4030	0.3733
Mono-(2-ethyl-5-hydroxyhexyl) phthalate	0.4667	0.3650	0.9343	0.6533	0.5891	0.3988	1.0000	0.5595	0.9763	0.5527
Mono-isobutyl phthalate	0.4057	0.3619	0.5337	0.7551	0.4467	0.4076	0.5595	1.0000	0.5778	0.5916
Mono-(2-ethyl-5-oxohexyl) phthalate	0.4850	0.3922	0.9416	0.6673	0.6081	0.4030	0.9763	0.5778	1.0000	0.5693
Mono-benzyl phthalate	0.3850	0.2986	0.5224	0.6875	0.4682	0.3733	0.5527	0.5916	0.5693	1.0000

Abbreviations: PHTHTEs: Phthalates and Plasticizers Metabolites  
PHTHTE subsample weights used

eTable 4. Comparison of demographics of included versus excluded participants for the (a) PAH and PHTHTE subsets and (b) VOC subset

a.

Variable	Excluded from PAH Subset		Included in PAH Subset		p-value	Excluded from PHTHTE Subset		Included in PHTHTE Subset		p-value
	N Missing	Statistics	N Missing	Statistics		N Missing	Statistics	N Missing	Statistics	
	N=14,897		N=7,090			N=14,963		N=7,024		
Female, % [95% CI]	0	49.9 (48.9, 50.9)	0	48.6 (47.2, 50.1)	0.19 <sup>c</sup>	0	49.4 (48.6, 50.3)	0	49.7 (48.3, 51.1)	0.78 <sup>c</sup>
Age at screening (y), mean [95% CI]	0	44.1 (43.5, 44.6)	0	43.4 (42.8, 44.0)	0.019 <sup>a</sup>	0	43.9 (43.4, 44.5)	0	43.7 (43.0, 44.3)	0.39 <sup>a</sup>
Race, % [95% CI]	0		0		0.81 <sup>c</sup>	0		0		0.31 <sup>c</sup>
Non-Hispanic white		63.3 (59.7, 66.7)		63.8 (60.2, 67.4)			63.4 (59.9, 66.8)		63.5 (59.9, 67.1)	
Non-Hispanic black		12.1 (10.5, 14.0)		11.7 (10.0, 13.6)			11.9 (10.2, 13.6)		12.3 (10.5, 14.3)	
Mexican-American		9.8 (8.1, 11.9)		9.6 (7.7, 11.9)			10.0 (8.2, 12.1)		9.3 (7.5, 11.2)	
Other		14.8 (13.1, 16.5)		14.8 (13.1, 16.5)			14.7 (13.1, 16.4)		14.9 (13.2, 16.7)	
Education level, % [95% CI]*	16		7		0.17 <sup>c</sup>	14		9		0.43 <sup>c</sup>
Less than High School		17.1 (15.6, 18.6)		15.8 (14.2, 17.6)			17.0 (15.5, 18.5)		16.0 (14.3, 17.7)	
High School/GED/Some College/AA		53.1 (51.6, 54.7)		53.2 (51.0, 55.3)			53.0 (51.5, 54.5)		53.4 (51.1, 55.7)	
College graduate+		29.8 (27.7, 32.0)		31.0 (28.4, 33.7)			30.0 (28.0, 32.1)		30.6 (27.8, 33.5)	
Health insurance, % [95% CI]*	13		9		0.005 <sup>c</sup>	15		7		0.21 <sup>c</sup>
None		21.0 (19.7, 22.5)		20.4 (18.8, 22.1)			21.0 (19.6, 22.5)		20.4 (18.8, 22.1)	
Private		61.2 (59.4, 63.1)		63.9 (61.5, 66.1)			61.6 (59.6, 63.6)		63.1 (61.0, 65.1)	
Other		17.7 (16.6, 18.9)		15.7 (14.4, 17.1)			17.4 (16.2, 18.6)		16.5 (15.3, 17.7)	
Marital status, % [95% CI]	8		3		0.20 <sup>c</sup>	8		3		0.28 <sup>c</sup>
Married/Widowed		58.0 (56.4, 59.5)		57.8 (55.7, 59.9)			57.4 (55.9, 58.9)		58.9 (56.7, 61.2)	
Separated/Divorced		12.1 (11.4, 12.9)		11.2 (10.2, 12.3)			12.0 (11.2, 12.8)		11.6 (10.6, 12.7)	
Never married/Living with partner		29.9 (28.2, 31.6)		31.0 (28.9, 33.1)			30.6 (29.0, 32.2)		29.5 (27.2, 31.8)	
Family PIR, mean [95% CI]*	1350	2.9 (2.9, 3.0)	648	3.0 (2.9, 3.1)	0.36 <sup>a</sup>	1356	2.9 (2.9, 3.0)	642	3.0 (2.9, 3.1)	0.46 <sup>a</sup>
Annual household income, % [95% CI]*	1364		656		0.16 <sup>c</sup>	1370		650		0.15 <sup>c</sup>
Under \$55,000		48.8 (46.4, 51.3)		48.3 (45.7, 50.9)			48.8 (46.4, 51.3)		48.3 (45.7, 50.9)	
\$55,000 - \$99,999		25.8 (24.3, 27.3)		24.8 (23.1, 26.6)			25.8 (24.4, 27.3)		24.7 (22.8, 26.7)	
\$100,000 and up		25.4 (23.0, 27.8)		26.9 (24.2, 29.7)			25.3 (23.0, 27.8)		27.0 (24.3, 29.8)	
Body Mass Index (kg/m <sup>2</sup> ), mean [95% CI]	201	28.4 (28.2, 28.6)	59	28.5 (28.3, 28.7)	0.39 <sup>a</sup>	198	28.4 (28.2, 28.6)	62	28.5 (28.3, 28.8)	0.28 <sup>a</sup>
Smoking status, % [95% CI]*	13		4		0.90 <sup>c</sup>	12		5		0.93 <sup>c</sup>
Never		58.0 (56.3, 59.6)		58.2 (56.4, 60.0)			58.1 (56.5, 59.6)		58.0 (56.0, 59.9)	
Past		21.4 (20.1, 22.7)		21.5 (20.2, 22.8)			21.5 (20.2, 22.8)		21.3 (19.9, 22.6)	
Current		20.7 (19.5, 21.9)		20.3 (18.9, 21.8)			20.5 (19.4, 21.6)		20.8 (19.1, 22.5)	
Dietary fiber (gm), mean [95% CI]*	1181	17.3 (17.0, 17.6)	522	17.4 (17.0, 17.7)	0.80 <sup>a</sup>	1211	17.3 (17.0, 17.6)	492	17.4 (17.0, 17.7)	0.63 <sup>a</sup>



HEI-2015 Score, mean [95% CI]	3082	53.9 (53.5, 54.4)	1409	54.2 (53.7, 54.7)	0.32 <sup>a</sup>	3144	54.0 (53.5, 54.4)	1347	54.1 (53.5, 54.7)	0.69 <sup>a</sup>
PHQ-9 Depression Severity, % [95% CI]*	1716		737		0.098 <sup>c</sup>	1721		732		0.28 <sup>c</sup>
None to Mild 0-9		93.0 (92.4, 93.6)		93.8 (92.9, 94.6)			93.1 (92.5, 93.7)		93.6 (92.8, 94.4)	
Moderate to Severe 10+		7.0 (6.4, 7.6)		6.2 (5.4, 7.1)			6.9 (6.3, 7.5)		6.4 (5.6, 7.2)	
Any vigorous or moderate activities, % [95% CI]*	6	73.5 (72.4, 74.7)	3	74.2 (72.5, 75.9)	0.42 <sup>c</sup>	6	73.5 (72.3, 74.7)	3	74.3 (72.6, 76.0)	0.39 <sup>c</sup>
Creatinine, urine (mg/dL), mean [95% CI]*	469	125.2 (122.6, 127.7)	3	119.4 (117.0, 121.9)	<0.001 <sup>a</sup>	470	122.6 (120.1, 125.1)	2	124.8 (122.0, 127.6)	0.12 <sup>a</sup>

Frequencies presented are unweighted counts.

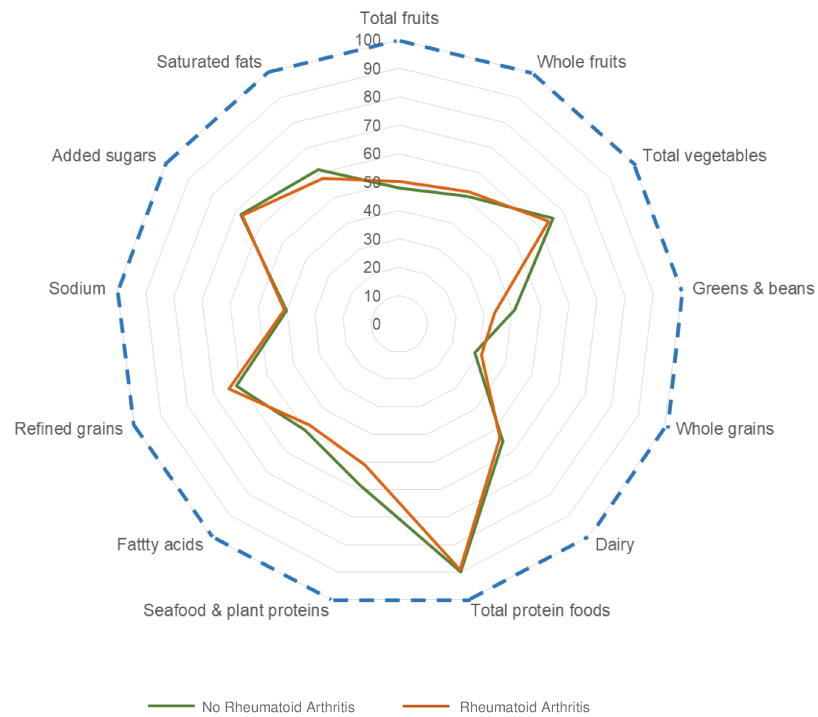
P-values: a=linear regression; c=Rao-Scott chi-square test.

SAS Survey Procedures with MEC weights used for all analyses.

b.

Variable	Excluded from VOC Subset		Included in VOC Subset		p-value
	N=14,858		N=7,129		
	N Missing	Statistics	N Missing	Statistics	
Female, % [95% CI]	0	50.1 (49.2, 51.1)	0	48.2 (46.9, 49.5)	0.029 <sup>c</sup>
Age at screening (y), mean [95% CI]	0	43.9 (43.2, 44.5)	0	43.8 (43.2, 44.4)	0.93 <sup>a</sup>
Race, % [95% CI]	0		0		0.25 <sup>c</sup>
Non-Hispanic white		63.5 (59.8, 67.0)		63.4 (59.2, 67.5)	
Non-Hispanic black		12.4 (10.6, 14.4)		11.2 (9.3, 13.4)	
Mexican-American		9.3 (7.6, 11.2)		10.8 (8.4, 13.7)	
Other		14.9 (13.2, 16.7)		14.5 (12.7, 16.6)	
Education level, % [95% CI]*	18		5		0.80 <sup>c</sup>
Less than High School		16.7 (15.2, 18.3)		16.6 (14.8, 18.6)	
High School/GED/Some College/AA		52.9 (51.2, 54.6)		53.7 (51.5, 55.9)	
College graduate+		30.4 (28.2, 32.7)		29.7 (26.9, 32.6)	
Health insurance, % [95% CI]*	13		9		0.74 <sup>c</sup>
None		21.0 (19.6, 22.5)		20.4 (18.6, 22.4)	
Private		62.0 (60.1, 64.0)		62.2 (59.5, 64.8)	
Other		16.9 (15.7, 18.2)		17.4 (16.1, 18.8)	
Marital status, % [95% CI]	8		3		0.88 <sup>c</sup>
Married/Widowed		58.0 (56.1, 59.8)		57.8 (55.9, 59.7)	
Separated/Divorced		11.7 (11.0, 12.5)		12.1 (11.0, 13.3)	
Never married/Living with partner		30.3 (28.3, 32.3)		30.1 (28.1, 32.1)	
Family PIR, mean [95% CI]*	1408	3.0 (2.9, 3.0)	590	2.9 (2.8, 3.0)	0.83 <sup>a</sup>
Annual household income, % [95% CI]*	1433		587		0.98 <sup>c</sup>
Under \$55,000		48.6 (46.0, 51.2)		48.8 (45.7, 51.9)	
\$55,000 - \$99,999		25.6 (23.9, 27.3)		25.3 (23.7, 27.0)	

\$100,000 and up		25.9 (23.2, 28.7)		25.9 (23.0, 28.9)	
Body Mass Index (kg/m <sup>2</sup> ), mean [95% CI]	186	28.4 (28.2, 28.6)	74	28.5 (28.3, 28.8)	0.33 <sup>a</sup>
Smoking status, % [95% CI]*	14		3		0.38 <sup>c</sup>
Never		58.1 (56.4, 59.7)		58.0 (55.9, 60.0)	
Past		21.1 (19.7, 22.4)		22.1 (20.7, 23.6)	
Current		20.9 (19.7, 22.1)		19.9 (18.4, 21.4)	
Dietary fiber (gm), mean [95% CI]*	1231	17.4 (17.2, 17.7)	472	17.1 (16.6, 17.5)	0.096 <sup>a</sup>
HEI-2015 Score, mean [95% CI]	3066	54.1 (53.6, 54.5)	1425	53.9 (53.3, 54.5)	0.60 <sup>a</sup>
PHQ-9 Depression Severity, % [95% CI]*	1802		651		0.44 <sup>c</sup>
None to Mild 0-9		93.2 (92.5, 93.8)		93.5 (92.7, 94.3)	
Moderate to Severe 10+		6.8 (6.2, 7.5)		6.5 (5.7, 7.3)	
Any vigorous or moderate activities, % [95% CI]*	4	73.5 (72.3, 74.6)	5	74.4 (72.8, 76.0)	0.24 <sup>c</sup>
Creatinine, urine (mg/dL), mean [95% CI]*	384	124.3 (121.5, 127.0)	88	121.2 (118.7, 123.8)	0.062 <sup>a</sup>

**eFigure 1. Diet quality by group as measured by HEI-2015 (per participant)**

The radar plot is representative of participants who participated in both days of the interview and is similar to an average across the two interview days.

The dotted blue line (---) depicts a perfect 100 point score.

Points closer to the outer edge represent a food pattern that is closer to meeting dietary recommendations.

Points closer to the center of the graph represent a food pattern that has room for improvement.

eTable 5. Stepwise adjustment analysis for each of the variables.

Factor	Adjustment 1		Adjustment 2		Adjustment 3		Adjustment 4		Adjustment 5	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Age (1 year increment)	1.07 (1.06, 1.08)	<0.001	1.07 (1.06, 1.08)	<0.001	1.07 (1.06, 1.08)	<0.001	1.07 (1.06, 1.08)	<0.001	1.07 (1.06, 1.08)	<0.001
Female vs. Male	1.8 (1.2, 2.5)	<b>0.002</b>	1.7 (1.2, 2.4)	<b>0.005</b>	1.6 (1.2, 2.4)	<b>0.007</b>	1.7 (1.2, 2.5)	<b>0.006</b>	1.5 (1.05, 2.3)	<b>0.029</b>
Creatinine, urine (1 mg/dL increment)	---	---	1.00 (1.00, 1.00)	0.75	1.00 (1.00, 1.00)	0.32	1.00 (1.00, 1.00)	0.48	1.00 (1.00, 1.00)	0.30
BMI (1 kg/m <sup>2</sup> increment)	---	---	---	---	1.05 (1.03, 1.08)	<0.001	1.05 (1.03, 1.08)	<0.001	1.05 (1.02, 1.08)	<0.001
Smoking										
Current vs. Never	---	---	---	---	---	---	1.4 (0.89, 2.3)	0.13	1.3 (0.77, 2.1)	0.35
Past vs. Never	---	---	---	---	---	---	1.03 (0.60, 1.8)	0.92	1.04 (0.60, 1.8)	0.88
Race										
Mexican-American vs. Non-Hispanic White	---	---	---	---	---	---	---	---	1.4 (0.77, 2.6)	0.27
Non-Hispanic Black vs. Non-Hispanic White	---	---	---	---	---	---	---	---	1.5 (1.01, 2.1)	<b>0.045</b>
Other vs. Non-Hispanic White	---	---	---	---	---	---	---	---	0.84 (0.48, 1.5)	0.54
High school or less vs. More than high school education	---	---	---	---	---	---	---	---	1.06 (0.71, 1.6)	0.78
Family poverty income ratio (1 unit increment)	---	---	---	---	---	---	---	---	0.90 (0.78, 1.04)	0.14
Any moderate and/or vigorous activity	---	---	---	---	---	---	---	---	0.96 (0.64, 1.4)	0.84
Dietary fiber (1 gm increment)	---	---	---	---	---	---	---	---	0.98 (0.95, 1.02)	0.34
PAH Body Burden										
Quartile 2 vs. 1	1.5 (0.91, 2.4)	0.11	1.5 (0.89, 2.5)	0.13	1.5 (0.89, 2.6)	0.13	1.5 (0.87, 2.5)	0.15	1.5 (0.87, 2.5)	0.15
Quartile 3 vs. 1	1.9 (1.2, 3.1)	<b>0.012</b>	1.9 (1.2, 3.2)	<b>0.013</b>	1.9 (1.1, 3.3)	<b>0.016</b>	1.8 (1.03, 3.0)	<b>0.039</b>	1.7 (0.97, 3.0)	0.066
Quartile 4 vs. 1	2.6 (1.5, 4.4)	<0.001	2.7 (1.4, 4.9)	<b>0.002</b>	2.8 (1.5, 5.0)	<b>0.001</b>	2.2 (1.2, 4.4)	<b>0.018</b>	2.2 (1.09, 4.2)	<b>0.028</b>

---: Not available; Factor not included in the adjustment

PAH subset (n = 7,090) with PAH subsample weights used for analysis

PAH Burden Score includes: 1-hydroxynaphthalene, 2-hydroxynaphthalene, 3-hydroxyfluorene, 2-hydroxyfluorene, 1-hydroxyphenanthrene, and 1-hydroxypyrene

All models were fitted on each of the 5 imputed datasets and parameter estimates were combined using SAS Mianalyze.

**eTable 6. Mediation criteria for PAH body burden**

Mediation Criteria	OR (95% CI)	p-value	Met Mediation Criteria
Smoking is associated with RA*	1.7 (1.3, 2.3)	<0.001	Yes
Smoking is associated with PAH body burden†	87.2 (43.9, 172.8)	<0.001	Yes
PAH body burden is associated with RA after adjusting for smoking†	2.2 (1.09, 4.2)	<b>0.028</b>	Yes

Abbreviations: OR: Odds Ratio; RA: Rheumatoid Arthritis; PAH: Polycyclic Aromatic Hydrocarbons

**Bold** = Significant with p<0.05

\*Current vs. Never/Past

†Q4 vs. Q1

Model included age, sex (Male vs. Female), race (non-Hispanic White vs. non-Hispanic Black vs. Mexican-American vs. Other), education (high school or less vs. more than high school), family PIR, BMI, urine creatinine, any vigorous or moderate activity (yes vs. no), and dietary fiber.

**eTable 7. Sensitivity analysis examining the associations between PAH body burden quartile and rheumatoid arthritis among never smoker participant subset**

Variable	Adjustment 1		Adjustment 2	
	OR [95% CI]	p-value	OR [95% CI]	p-value
PAH body burden quartile				
Quartile 2 vs 1	1.6 [0.81, 3.0]	0.18	1.5 [0.71, 3.3]	0.27
Quartile 3 vs 1	2.5 [1.3, 5.1]	<b>0.008</b>	2.2 [0.90, 5.4]	0.082
Quartile 4 vs 1	3.0 [1.3, 7.1]	<b>0.013</b>	2.5 [0.86, 7.1]	0.092

**Bold** = Significant with p<0.05

Abbreviations: PIR: Poverty Income Ratio; PAH: Polycyclic Aromatic Hydrocarbons; OR: odds ratio

PAH never smokers subset (n = 4,102) with PAH subsample weights used for analysis

PAH Burden Score includes: 1-hydroxynaphthalene, 2-hydroxynaphthalene, 3-hydroxyfluorene, 2-hydroxyfluorene, 1-hydroxyphenanthrene, and 1-hydroxypyrene.

Adjustment 1: Adjusted for age and sex (male vs. female).

Adjustment 2: Adjusted for age, sex (male vs. female), BMI, urine creatinine, race (non-Hispanic white vs. non-Hispanic black vs. Mexican-American vs. other), education (high school or less vs. more than high school), family PIR, any vigorous or moderate activity (yes vs. no), and dietary fiber.

All models were fitted on each of the 5 imputed datasets and parameter estimates were combined using SAS Mianalyze.