Environ Health Perspect

DOI: 10.1289/EHP11814

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Supplemental Material

Environmental Exposure to Emerging Alternatives of Per- and Polyfluoroalkyl Substances and Polycystic Ovarian Syndrome in Women Diagnosed with Infertility: A Mixture Analysis

Wenqiang Zhan, Wei Qiu, Yan Ao, Wei Zhou, Yun Sun, Han Zhao, and Jun Zhang

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Figure S6. Bivariate exposure-response associations between the PFAS and PCOS from BKMR model (n = 943) (see Excel Table S7 for corresponding numeric data). Estimates were adjusted for age (linear), BMI (categorical), annual household income (categorical), educational level (categorical), study site (categorical), age at menarche (linear) and menstrual volume (categorical). Bivariate exposure-response functions for one PFAS when another PFAS fixed at either the 25th, 50th, or 75th percentile and the remaining PFAS are fixed at the median. For full chemical names see Table 1.

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Additional File- Excel Document

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PFASa	aroun	All subjects	sa (n = 943)	Normal weig	ght $(n = 622)$	= 622)					
ITAS	group	gPIP	cPIP	gPIP	cPIP	gPIP	cPIP				
n-PFHxS	2	0.107	0.125	0.016	0.329	0.122	0.019				
br-PFHxS	2	0.107	0.136	0.016	0.212	0.122	0.196				
n-PFOS	2	0.107	0.042	0.016	0.109	0.122	0.015				
6m-PFOS	2	0.107	0.095	0.016	0.135	0.122	0.307				
1m-PFOS	2	0.107	0.146	0.016	0.126	0.122	0.011				
\sum 3,4,5m-PFOS	2	0.107	0.456	0.016	0.089	0.122	0.452				
PFOA	1	0.616	0.029	0.045	0.025	0.872	0.012				
PFNA	1	0.616	0.005	0.045	0.001	0.872	0.002				
PFDA	1	0.616	0.012	0.045	0.011	0.872	0.007				
PFHpS	1	0.616	0.006	0.045	0.002	0.872	0.009				
PFDOA	1	0.616	0.109	0.045	0.042	0.872	0.102				
PFUDA	1	0.616	0.007	0.045	0.015	0.872	0.014				
6:2 Cl-PFESA	1	0.616	0.642	0.045	0.656	0.872	0.695				
8:2 Cl-PFESA	1	0.616	0.006	0.045	0.049	0.872	0.002				
HFPO-DA	1	0.616	0.126	0.045	0.112	0.872	0.099				
PFBS	1	0.616	0.019	0.045	0.026	0.872	0.012				
PFBA	1	0.616	0.005	0.045	0.001	0.872	0.006				
PFPeS	1	0.616	0.012	0.045	0.016	0.872	0.005				
PFPeA	1	0.616	0.007	0.045	0.005	0.872	0.001				
PFHxA	1	0.616	0.009	0.045	0.015	0.872	0.022				
PFHpA	1	0.616	0.004	0.045	0.024	0.872	0.012				

Table S1. Estimated posterior inclusion probability for PFAS in relation to the risk of PCOS in BKMR analyses (n = 943).

Notes: PFAS were ln-transformed. gPIP: group posterior inclusion probability; cPIP: conditional posterior inclusion probability. Groups with PIP>0.5 were empirically regarded as important to outcome specific association. But the relative importance of a specific chemical within the group was determined by the rank of PIPs in that group.

^a For full chemical names see Table 1.

	PCOS (n=299)	Non-PCOS (n=531)	Adjusted OR ^b	D 1 *
PFAS (ng/mL)"	Median (P25-P75)	Median (P25-P75)	(95% CI)	<i>P</i> -value
Legacy PFAS				
PFOA	8.68 (5.43-15.2)	7.18 (3.73-13.2)	1.05 (0.76-1.29)	0.57
T-PFOS	5.09 (3.73-7.68)	4.03 (2.79-6.70)	1.27 (0.98-1.52)	0.06
PFNA	0.93 (0.58-1.54)	0.82 (0.44-1.42)	1.02 (0.81-1.25)	0.65
PFDA	0.94 (0.60-1.58)	0.74 (0.34-1.45)	1.15 (0.89-1.35)	0.70
T-PFHxS	0.30 (0.17-0.65)	0.21 (0.10-0.52)	1.06 (0.78-1.32)	0.76
PFHpS	0.09 (0.06-0.15)	0.08 (0.05-0.13)	1.13 (0.94-1.27)	0.27
PFDOA	0.14 (0.11-0.19)	0.11 (0.08-0.17)	1.32 (1.20-1.51)	0.006
PFUDA	0.66 (0.44-1.21)	0.51 (0.24-1.10)	1.07 (0.72-1.29)	0.50
PFAS isomers				
n-PFHxS	0.31 (0.21-0.51)	0.22 (0.12-0.38)	1.09 (0.87-1.30)	0.72
br-PFHxS	0.03 (0.01-0.04)	0.01 (0.01-0.02)	1.12 (0.96-1.36)	0.07
n-PFOS	4.33 (2.58-7.52)	3.46 (1.83-6.71)	1.35 (1.09-1.67)	0.003
6m-PFOS	0.39 (0.21-0.63)	0.31 (0.15-0.48)	1.28 (0.95-1.47)	0.65
1m-PFOS	0.16 (0.11;0.22)	0.12 (0.08;0.20)	1.15 (1.05-1.37)	0.02
∑3,4,5m-PFOS	0.60 (0.38-1.11)	0.51 (0.26-0.96)	1.31 (1.12-1.56)	0.0007
PFAS alternatives				
6:2 Cl-PFESA	3.63 (2.52-6.39)	2.59 (1.18-6.06)	1.21 (1.06-1.37)	0.0002
8:2 Cl-PFESA	0.10 (0.07-0.15)	0.06 (0.03-0.14)	1.05 (0.78-1.24)	0.37
HFPO-DA	0.04 (0.03-0.07)	0.02 (0.01-0.04)	1.39 (1.21-1.75)	0.001
Short-chain PFAS				
PFBS	0.06 (0.03-0.10)	0.05 (0.03-0.09)	0.94 (0.71-1.24)	0.106
PFBA	0.94 (0.60-1.58)	0.74 (0.34-1.45)	0.85 (0.71-1.00)	0.05
PFPeS	0.01 (0.01-0.01)	0.01 (0.00-0.01)	1.16 (1.04-1.32)	0.04
PFPeA	0.04 (0.02-0.10)	0.02 (0.01-0.06)	1.07 (0.72-1.32)	0.22
PFHxA	0.02 (0.02-0.03)	0.01 (0.01-0.01)	1.16 (1.05-1.31)	0.01
PFHpA	0.07 (0.05-0.11)	0.05 (0.03-0.08)	1.09 (0.91-1.20)	0.18

Table S2. Associations of ln-transformed PFAS concentration with PCOS-related infertility in logistic regression model among participants with normal menstrual volume (n = 830).

Abbreviations: OR, odds ratio; CI, confidence interval; PCOS, polycystic ovarian syndrome. Note: PBAC scoring ≥ 100 was considered as hypomenorrhea, PBAC <10 was considered as menorrhagia, and PBAC scoring 10 – 99 was considered as normal menstrual volume. *The *p*-value indicated the significance of the association between ln-transformed PFAS concentration and PCOS in logistic regression model.

^a For full chemical names see Table 1.

Table S3.	Associations	of	In-transformed	PFAS	concentration	with	PCOS-related	infertility	in	logistic
regression	model among	g nư	illiparous wome	en (n =	792).					

	PCOS (n=300)	Non-PCOS (n=492)	Adjusted OR ^b	
PFA5"	Median (P25-P75)	Median (P25-P75)	(95% CI)	<i>p</i> -value
Legacy PFAS				
PFOA	8.46 (5.13-14.1)	7.02 (3.70-12.8)	1.08 (0.94-1.24)	0.62
T-PFOS	4.85 (3.64-7.38)	4.02 (2.77-6.64)	1.17 (0.92-1.31)	0.09
PFNA	0.88 (0.56-1.36)	0.81 (0.42-1.41)	1.12 (0.72-1.74)	0.57
PFDA	0.88 (0.55-1.50)	0.73 (0.35-1.46)	1.02 (0.72-1.44)	0.25
T-PFHxS	0.30 (0.17-0.61)	0.21 (0.11-0.51)	1.10 (0.78-1.57)	0.86
PFHpS	0.09 (0.06-0.15)	0.08 (0.05-0.13)	0.95 (0.61-1.46)	0.41
PFDOA	0.14 (0.11-0.19)	0.11 (0.08-0.17)	1.32 (1.18-1.56)	0.003
PFUDA	0.64 (0.41-1.16)	0.51 (0.24-1.11)	1.24 (0.81-1.61)	0.56
PFAS isomers				
n-PFHxS	0.30 (0.21-0.50)	0.22 (0.12-0.38)	1.08 (0.95-1.23)	0.69
br-PFHxS	0.03 (0.01-0.04)	0.01 (0.01-0.02)	1.19 (0.97-1.36)	0.16
n-PFOS	3.94 (2.43-7.16)	3.41 (1.81-6.68)	1.26 (1.08-1.46)	0.02
6m-PFOS	0.38 (0.21-0.61)	0.31 (0.16-0.48)	1.12 (0.97-1.30)	0.22
1m-PFOS	0.15 (0.11-0.22)	0.12 (0.08-0.20)	1.25 (1.12-1.47)	0.01
\sum 3,4,5m-PFOS	0.57 (0.38-1.11)	0.49 (0.26-0.96)	1.29 (1.16-1.63)	0.0009
PFAS alternatives				
6:2 Cl-PFESA	3.66 (2.49-6.00)	2.57 (1.16-6.00)	1.31 (1.11-1.52)	0.0002
8:2 Cl-PFESA	0.10 (0.07-0.15)	0.06 (0.03-0.14)	1.15 (0.97-1.28)	0.15
HFPO-DA	0.04 (0.03-0.07)	0.02 (0.01-0.04)	1.23 (1.06-1.47)	0.003
Short-chain PFAS				
PFBS	0.06 (0.03-0.10)	0.05 (0.03-0.09)	0.93 (0.71-1.22)	0.26
PFBA	0.09 (0.06-0.12)	0.08 (0.06-0.11)	0.87 (0.73-1.05)	0.19

PFPeS	0.01 (0.01-0.01)	0.01 (0.00-0.01)	1.09 (0.97-1.26)	0.29
PFPeA	0.04 (0.02-0.09)	0.02 (0.01-0.06)	0.98 (0.83-1.16)	0.62
PFHxA	0.02 (0.02-0.03)	0.01 (0.01-0.01)	1.21 (1.08-1.42)	0.02
PFHpA	0.07 (0.05-0.11)	0.05 (0.03-0.08)	1.09 (0.84-1.40)	0.27

Abbreviations: OR, odds ratio; CI, confidence interval; PCOS, polycystic ovarian syndrome. Note: Parity was determined based on the medical records by trained researchers.

*The *p*-value indicated the significance of the association between ln-transformed PFAS

concentration and PCOS in logistic regression model.

^a For full chemical names see Table 1.

^b Adjusted for age (linear), BMI (categorical), annual household income (categorical), educational level (categorical), study site (categorical), age at menarche (linear) and menstrual volume (categorical).

Table S4. Odds ratios (OR) and 95%CI confidence interval (CIs) for polycystic ovary syndrome (PCOS) in tertiles of PFAS alternatives in logistic regression model (n = 943).

PFAS ^a tertiles (ng/mL)	Adjusted OR ^b (95%CI)
6:2 Cl-PFESA	
Q1 (<2.72)	Ref
Q2 (2.72-4.86)	1.26 (1.08-1.56)
Q3 (≥4.86)	1.46 (1.15-1.79)
8:2 Cl-PFESA	
Q1 (<0.06)	Ref
Q2 (0.06-0.12)	0.86 (0.69-1.11)
Q3 (≥0.12)	1.12 (0.98-1.32)
HFPO-DA	
Q1 (<0.02)	Ref
Q2 (0.02-0.04)	1.19 (1.07-1.41)
Q3 (≥0.04)	1.45 (1.19-1.71)

Note: The tertiles are defined as all participants were divided equally into three equal parts, with 314 (Q1), 315 (Q2) and 314 (Q3) participants in each of the three parts.

^a For full chemical names see Table 1.

PFAS ^a tertiles (ng/mL)	Adjusted OR ^b (95%CI)
PFOA	
Q1 (<6.29)	Ref
Q2 (6.29-10.86)	1.07 (0.90-1.19)
Q3 (≥10.86)	1.20 (0.95-1.36)
T-PFOS	
Q1 (<3.87)	Ref
Q2 (3.87-5.85)	1.09 (0.82-1.25)
Q3 (≥5.85)	1.19 (1.02-1.41)
PFNA	
Q1 (<0.69)	Ref
Q2 (0.69-1.18)	1.09 (0.89-1.22)
Q3 (≥1.18)	1.15 (0.95-1.41)
PFDA	
Q1 (<0.66)	Ref
Q2 (0.66-1.17)	0.97 (0.82-1.13)
Q3 (≥1.17)	1.05 (0.91-1.16)
PFHpS	
Q1 (<0.07)	Ref
Q2 (0.07-0.11)	0.91 (0.75-1.07)
Q3 (≥0.11)	1.06 (0.90-1.21)
T-PFHxS	
Q1 (<0.20)	Ref
Q2 (0.20-0.43)	1.09 (0.94-1.25)
Q3 (≥0.43)	1.21 (1.05-1.39)
PFDoA	
Q1 (<0.11)	Ref
Q2 (0.11-0.16)	1.27 (1.09-1.41)
Q3 (≥0.16)	1.46 (1.22-1.65)
PFUdA	
Q1 (<0.46)	Ref
Q2 (0.46-0.89)	1.11 (0.84-1.21)
Q3 (≥0.89)	1.21 (0.98-1.40)

Table S5. Odds ratios (OR) and 95%CI confidence interval (CIs) for polycystic ovary syndrome (PCOS) in tertiles of legacy PFAS in logistic regression model (n = 943).

Note: The tertiles are defined as all participants were divided equally into three equal parts, with 314 (Q1), 315 (Q2) and 314 (Q3) participants in each of the three parts.

^a For full chemical names see Table 1.

PFAS ^a tertiles (ng/mL)	Adjusted OR ^b (95%CI)
n-PFHxS	
Q1 (<0.21)	Ref
Q2 (0.21-0.35)	1.12 (0.87-1.29)
Q3 (≥0.35)	1.21 (0.95-1.42)
br-PFHxS	
Q1 (<0.02)	Ref
Q2 (0.02-0.03)	1.15 (0.82-1.31)
Q3 (≥0.03)	1.39 (1.03-1.62)
n-PFOS	
Q1 (<2.98)	Ref
Q2 (2.98-5.63)	1.09 (0.87-1.25)
Q3 (≥5.63)	1.17 (1.02-1.39)
6m-PFOS	
Q1 (<0.29)	Ref
Q2 (0.29-0.46)	1.10 (0.87-1.26)
Q3 (≥0.46)	1.08 (0.79-1.21)
1m-PFOS	
Q1 (<0.12)	Ref
Q2 (0.12-0.18)	1.12 (0.85-1.29)
Q3 (≥0.18)	1.31 (0.97-1.46)
\sum 3,4,5m-PFOS	
Q1 (<0.43)	Ref
Q2 (0.43-0.79)	1.22 (1.05-1.48)
Q3 (≥0.79)	1.45 (1.24-1.72)

Table S6. Odds ratios (OR) and 95%CI confidence interval (CIs) for polycystic ovary syndrome (PCOS) in tertiles of PFAS isomers in logistic regression model (n = 943).

Note: The tertiles are defined as all participants were divided equally into three equal parts, with 314 (Q1), 315 (Q2) and 314 (Q3) participants in each of the three parts.

^a For full chemical names see Table 1.

PFAS ^a tertiles (ng/mL)	Adjusted OR ^b (95%CI)
PFBS	
Q1 (<0.04)	Ref
Q2 (0.04-0.08)	0.92 (0.72-1.09)
Q3 (≥0.08)	1.07 (0.87-1.22)
PFHpA	
Q1 (<0.05)	Ref
Q2 (0.05-0.08)	1.06 (0.82-1.16)
Q3 (≥0.08)	1.24 (0.90-1.41)
PFPeA	
Q1 (<0.02)	Ref
Q2 (0.02-0.06)	1.02 (0.79-1.15)
Q3 (≥0.06)	1.09 (0.86-1.20)
PFPeS	
Q1 (<0.007)	Ref
Q2 (0.007-0.012)	1.07 (0.85-1.27)
Q3 (≥0.012)	1.17 (1.05-1.32)
PFBA	
Q1 (<0.07)	Ref
Q2 (0.07-0.10)	0.82 (0.67-1.09)
Q3 (≥0.10)	0.91 (0.72-1.15)
PFHxA	
Q1 (<0.01)	Ref
Q2 (0.01-0.02)	1.21 (1.09-1.41)
Q3 (≥0.02)	1.42 (1.16-1.65)

Table S7. Odds ratios (OR) and 95%CI confidence interval (CIs) for polycystic ovary syndrome (PCOS) in tertiles of short-chain PFAS in logistic regression model (n = 943).

Note: The tertiles are defined as all participants were divided equally into three equal parts, with 314 (Q1), 315 (Q2) and 314 (Q3) participants in each of the three parts.

^a For full chemical names see Table 1.



Fig. S1. Participants selection framework. Abbreviations: PCOS, polycystic ovarian syndrome; AID, artificial insemination with donor sperm.



Fig. S2. Directed Acyclic Graph for covariate selection. Abbreviations: PCOS, polycystic ovarian syndrome.

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			_	 		-							<u> </u>			5			<u>`</u>					
Г		1.00	0.40	0.33	0.21	0.19	0.10	0.43	0.43	0.48	0.42	0.35	0.28	0.07	0.05	0.06	0.24	0.12	0.23	0.24	0.06	0.01	8:2 CL PEES A	
	Г	0.40	1.00	0.70	0.40	0.48	0.29	0.48	0.47	0.50	0.64	0.38	0.40	0.19	0.04	0.04	0.23	0.13	0.14	0.11	0.06	0.01	∑3,4,5 	
	L	0.33	0.70	1.00	0.41	0.47	0.31	0.41	0.39	0.48	0.62	0.32	0.37	0.26	0.09	0.10	0.16	0.13	0.13	0.02	0.06	0.02	1m-PFOS 0.6	
	1_	0.21	0.40	0.41	1.00	0.60	0.32	0.36	0.42	0.35	0.51	0.31	0.39	0.13	0.21	0.11	0.12	0.17	0.22	0.10	0.04	0.02	0.4 PFHpS	
	14	0.19	0.48	0.47	0.60	1.00	0.47	0.47	0.50	0.43	0.57	0.44	0.46	0.23	0.30	0.23	0.28	0.50	0.39	0.10	0.10	0.11	n-PFHxS 0.2	
4		0.10	0.29	0.31	0.32	0.47	1.00	0.46	0.48	0.44	0.46	0.37	0.48	0.17	0.14	0.13	0.14	0.20	0.23	0.04	0.19	0.10	PFOA 0	
	Ι.	0.43	0.48	0.41	0.36	0.47	0.46	1.00	0.87	0.81	0.78	0.70	0.64	0.25	0.10	0.03	0.21	0.29	0.25	0.03	0.11	0.08	PFDA	
	ļβ	0.43	0.47	0.39	0.42	0.50	0.48	0.87	1.00	0.72	0.75	0.72	0.67	0.22	0.09	0.06	0.20	0.24	0.25	0.03	0.10	0.05	PFUnDA	
		0.48	0.50	0.48	0.35	0.43	0.44	0.81	0.72	1.00	0.81	0.55	0.52	0.25	0.07	0.03	0.19	0.23	0.23	0.03	0.07	0.08	6:2 Cl-PFESA	
	ЦĽ	0.42	0.64	0.62	0.51	0.57	0.46	0.78	0.75	0.81	1.00	0.55	0.58	0.25	0.08	0.05	0.15	0.25	0.20	0.02	0.07	0.04	n-PFOS	
		0.35	0.38	0.32	0.31	0.44	0.37	0.70	0.72	0.55	0.55	1.00	0.54	0.14	0.22	0.16	0.33	0.31	0.33	0.05	0.17	0.13	PFDoA	
	Ľ	0.28	0.40	0.37	0.39	0.46	0.48	0.64	0.67	0.52	0.58	0.54	1.00	0.22	0.05	0.08	0.13	0.15	0.20	-0.01	0.03	0.02	PFNA 6m-PFOS	
		0.07	0.19	0.26	0.13	0.23	0.17	0.25	0.22	0.25	0.25	0.14	0.22	1.00	0.02	-0.01	0.03	0.14	0.05	-0.11	0.02	-0.06		
		0.05	0.04	0.09	0.21	0.30	0.14	0.10	0.09	0.07	0.08	0.22	0.05	0.02	1.00	0.45	0.25	0.31	0.41	0.15	0.20	0.19	PFBS	
	ΓL	0.06	0.04	0.10	0.11	0.23	0.13	0.03	0.06	0.03	0.05	0.16	0.08	-0.01	0.45	1.00	0.32	0.28	0.28	0.31	0.19	0.10	PFHpA	
٦٢	1	0.24	0.23	0.16	0.12	0.28	0.14	0.21	0.20	0.19	0.15	0.33	0.13	0.03	0.25	0.32	1.00	0.30	0.28	0.26	0.32	0.23	PFHxA	
	۱,	0.12	0.13	0.13	0.17	0.50	0.20	0.29	0.24	0.23	0.25	0.31	0.15	0.14	0.31	0.28	0.30	1.00	0.35	0.15	0.14	0.15	br-PFHxS	
4	۴	0.23	0.14	0.13	0.22	0.39	0.23	0.25	0.25	0.23	0.20	0.33	0.20	0.05	0.41	0.28	0.28	0.35	1.00	0.11	0.12	0.15	PFPeS	
		0.24	0.11	0.02	0.10	0.10	0.04	0.03	0.03	0.03	0.02	0.05	-0.01	-0.11	0.15	0.31	0.26	0.15	0.11	1.00	0.17	0.09	HFPO-DA	
4	_	0.06	0.06	0.06	0.04	0.10	0.19	0.11	0.10	0.07	0.07	0.17	0.03	0.02	0.20	0.19	0.32	0.14	0.12	0.17	1.00	0.20	PFBA	
ı	1	0.01	0.01	0.02	0.02	0.11	0.10	0.08	0.05	0.08	0.04	0.13	0.02	-0.06	0.19	0.10	0.23	0.15	0.15	0.09	0.20	1.00	PFPeA	
		8:2 CI-PI	∑3,4 FOS	In-F	PFH	n-PF	PFO.	PFD.	PFU	6:2 CI-PI	n-PF	PFD	PFN	6m-P	PFBS	PFH	PFH	br-Pf	PFPe	HFP	PFB.	PFPe		
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Fig. S3. Clustered heatmap of the spearman correlation matrix of PFAS (ln-transformed) (n = 943) (see Excel Tables S1 for corresponding numeric data). The numbers in the box are pairwise correlation coefficients. For full chemical names see Table 1.



Fig. S4. Clustered heatmap of the spearman correlation matrix of PFAS (ln-transformed) in PCOS cases (A) (n = 366) and controls (B) (n = 577) (see Excel Tables S2-3 for corresponding numeric data). The numbers in the box are pairwise correlation coefficients. For full chemical names see Table 1.







Fig. S5. Univariate exposure-response relationship between PFAS and the risk of PCOS (n = 943) (see Excel Tables S4 for corresponding numeric data). Estimates were adjusted for age (linear), BMI (categorical), annual household income (categorical), educational level (categorical), study site (categorical), age at menarche (linear) and menstrual volume (categorical). Curves were fitted via generalized additive model with restricted cubic spline (df = 4). For full chemical names see Table 1.

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Fig. S6. Bivariate exposure-response associations between the PFAS and PCOS from BKMR model (n = 943) (see Excel Table S7 for corresponding numeric data). Estimates were adjusted for age (linear), BMI (categorical), annual household income (categorical), educational level (categorical), study site (categorical), age at menarche (linear) and menstrual volume (categorical). Bivariate exposure-response functions for one PFAS when another PFAS fixed at either the 25th, 50th, or 75th percentile and the remaining PFAS are fixed at the median. For full chemical names see Table 1.



Fig. S7. Joint effect estimates with 95% CI for the PFAS mixture in relation to PCOS in the hierarchical BKMR models, stratified by BMI; all the chemicals at particular percentiles (from 0.25 to 0.75 increment by 0.05) were compared to all the chemicals at their 50th percentile (see Excel Tables S8-9 for corresponding numeric data). A: Normal weight group (n = 622); B: overweight/obese group (n = 321). All estimates were adjusted for age (continuous), BMI (categorical), annual household income (categorical), educational level (categorical), study site (categorical), age at menarche (continuous) and menstrual volume (categorical). The *P*-values indicated the significance of the association between PFAS mixture and PCOS in the BKMR model. Abbreviations: PCOS, polycystic ovarian syndrome.